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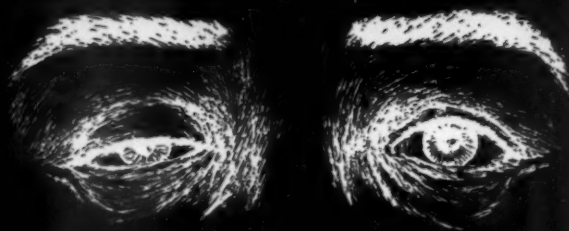
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1. Schwab, R.S.; Marshall, Clare K.; and Timberlake, William: *J.A.M.A.*, 158:625, June 25, 1955.

2. Schwab, R.S.: *Am. Jour. Med.*, 19:734, Nov., 1955.

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The American Journal of Medicine

Vol. XXIII SEPTEMBER, 1957 No. 3

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Editorial

The Syndrome of Alveolar Hypoventilation

ALFRED P. FISHMAN, GERARD M. TURINO AND EDWARD H. BERGOFKY 333

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Potassium Movement in Patients with Familial Periodic Paralysis. Relationship to the Defect in Muscle Function

DAVID GROB, RICHARD J. JOHNS AND ÅKE LILJESTRAND 356

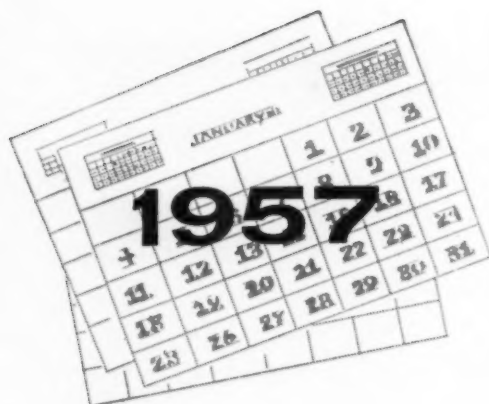
These papers deal with the movement of potassium into and out of the muscle cells of the forearm as deduced from simultaneous measurements of the potassium concentration in brachial artery and antecubital vein blood after the forearm muscles were exercised and after administration of potassium chloride, glucose, insulin and other compounds. The direction and magnitude of potassium movement in normal man was first studied. Exercise resulted in a loss of muscle potassium; administration of potassium increased the muscle potassium; glucose increased and insulin decreased the muscle potassium. Similar experiments in three patients with periodic paralysis showed an abnormally large uptake of potassium by muscle; excessive loss of potassium from contracting muscle during attacks; exaggerated movement of potassium into muscle after meals, glucose or insulin administration, with development of profound muscle weakness; hyperpolarization of the muscle membrane; reduction in muscle responsiveness to nerve stimulation, in propagation of excitation, and in contractility. The studies give some clue to the nature of the defect in familial periodic paralysis.

The Electrocardiogram and Potassium Metabolism. Electrocardiographic Abnormalities in Primary Aldosteronism and Familial Periodic Paralysis

F. S. P. VAN BUCHEM 376

A patient with primary aldosteronism, due to adrenal hyperplasia, was found to have a low serum potassium with related electrocardiographic changes, but no muscle paralysis and, indeed, a normal concentration of potassium in the skeletal muscle. Electrocardiographic abnormalities persisted long after the serum potassium level reverted to normal following adrenalectomy. In a patient with familial periodic paralysis, on the other hand, low serum potassium levels were associated both with paralytic attacks and electrocardiographic changes. The significance of these contrasting findings is discussed.

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VOLUME TWENTY-THREE

NUMBER THREE

Adynamia Episodica Hereditaria. A Disease Clinically Resembling Familial Periodic Paralysis but Characterized by Increasing Serum Potassium During the Paralytic Attacks

I. GAMSTORP, M. HAUGE, H. F. HELWEG-LARSEN, H. MJÖNES AND U. SAGILD 385

In a report of unusual interest the authors describe a newly defined inborn error of metabolism characterized by recurrent attacks of paralysis of the muscles of the extremities and the trunk, very much like those encountered in familial periodic paralysis. The serum potassium level during attacks is increased, however, probably due to leakage from the intracellular compartment of muscle since the urinary excretion of potassium does not decline. Unlike familial periodic paralysis, attacks are worsened or precipitated by administration of potassium salts, even in comparatively low dosage.

Potassium Deficiency of Renal and Adrenal Origin

R. V. BROOKS, R. R. MCSWINEY, F. T. G. PRUNTY AND F. J. Y. WOOD 391

The authors cite three well studied cases to demonstrate that certain sharply drawn syndromes characterized by potassium deficiency of renal and/or adrenal origin are not quite as distinct as has been implied. One case, proved to be due to an adrenal cortical carcinoma, gave overlapping clinical and metabolic indications of excessive secretion of aldosterone and simultaneously also of other steroids. Another case, presenting as renal tubular acidosis with nephrocalcinosis, was found at necropsy to be sarcoidosis. A third offered unusual problems in determining whether potassium loss should be ascribed to an intrinsic renal tubular defect or to primary adrenal dysfunction. The discussion as a whole reviews the issues involved most informatively.

Glycinuria, a Hereditary Disorder Associated with Nephrolithiasis

ANDRÉ DE VRIES, SHAUL KOCHWA, JACOB LAZEBNIK, MENAHEM FRANK
AND MEIR DJALDETTI 408

In a report of unusual interest, the authors record the familial occurrence of urinary excretion of glycine in unequivocal excess of the normal and without accompanying anomalies in the urinary excretion of any other amino acid or metabolite. It is made plain that the glycinuria is a reflection of deficient tubular reabsorption specifically of this amino acid. There appears to be an associated tendency to nephrolithiasis. The implication is that this disorder represents a new inborn error of metabolism of the group characterized by a specific defect in renal tubular reabsorption mechanisms.

Renal Clearance of Lysine in Cystinuria. Pathogenesis and Management of this Abnormality . P. D. DOOLAN, H. A. HARPER, M. E. HUTCHIN AND E. L. ALPEN 416

It is now securely established that the metabolic defect in cystinuria lies in defective renal tubular reabsorption of cystine, lysine, arginine and ornithine. Why these four amino acids should be so associated is a subject for speculation, and the principal topic of this study in which investigation of the renal disposition of lysine is made the point of departure. The experimental results and the interesting discussion throw light not only upon the pathogenesis of cystinuria but also of other inborn errors characterized by deficiencies of tubular transport systems, and, in addition, upon the general subject of tubular reabsorption of amino acids.

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*Ferguson, J. T., and Linn, F. V. Z.: Antibiotic Med. & Clin. Therapy 3:329, 1956.



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VOLUME TWENTY - THREE

NUMBER THREE

- Marfan's Syndrome. A Report of Three Patients with Aneurysm of the Aorta
ELIAS G. PAPPAS, DANIEL MASON AND CLARENCE DENTON 426

The association of arachnodactyly and other congenital anomalies with medial cystic necrosis of the aorta, and consequent aneurysm and dissection, is well known. Three interesting examples are cited, two with instructive necropsy findings.

- Marfan's Syndrome: Description of a Family RODMAN WILSON 434

The syndrome described by Marfan is now known to reflect an inborn error, presumably of metabolism, expressed as a widespread connective tissue defect. Skeletal, ligamentous and cardiovascular (notably aortic) anomalies predominate. The hereditary and clinical manifestations in an affected family are interestingly described in this report, which includes necropsy findings in a subject who died of cardiac failure resulting from aneurysmal dilatation of the root of the aorta with stretching of the aortic ring and aortic regurgitation. The syndrome is not so rare but what it deserves consideration under appropriate circumstances of differential diagnosis, and is certainly of considerably innate interest.

Review

- Renal Involvement in Progressive Systemic Sclerosis (Generalized Scleroderma)
GERALD P. RODMAN, GEORGE E. SCHREINER AND ROGER L. BLACK 445

The authors point out the frequent occurrence of morphologic changes in the kidney in progressive systemic sclerosis (scleroderma). These often are not accompanied by striking clinical or laboratory abnormalities suggestive of renal impairment, at least not until the terminal phase, hence are generally not appreciated during life. Nine cases are described, in seven the patients died in uremia which developed late in the disease. The renal lesions discovered at necropsy are characterized by intimal proliferation particularly of the interlobular arteries, fibrinoid necrosis and widespread focal cortical infarction. There is an interesting and well balanced discussion of the significance of these lesions, and of the possible role of steroid therapy in their causation.

Seminar on Atherosclerosis

- The Epidemiology of Coronary Heart Disease GEORGE V. MANN 463

In this timely and interesting article Dr. Mann takes a fresh look at the statistics relating to coronary heart disease. He gives sound reasons for questioning the validity of the apparent increase in recorded mortality due to heart disease in the United States from about 9 per cent in 1900 to almost 40 per cent in 1956; without, however, disproving that a substantial increase has occurred. The inadequacies of cause-of-death certification, particularly in sudden death, the effects of such factors as transference and medical sophistication, and of competing causes of death are discussed at length. All this, and more, Dr. Mann points out, bears upon current discussions of the role of dietary factors (analysis of which poses difficult problems indeed), occupation, activity, sex, ethnic background, in atherogenesis and coronary heart disease. These difficulties, of course, are multiplied when one attempts to compare specific disease mortality rates in one country with

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NUMBER THREE

those in another. The epidemiologic approach in chronic disease, it is concluded, is important but subject to such extraordinary complexities in fact finding and interpretation that much more work will be required before conclusions can be accepted with confidence.

Clinico-pathologic Conference

- Cholecystectomy Followed by Ascites, Fever and Oliguria 481
 Clinico-pathologic Conference (Washington University School of Medicine).

Case Reports

- An Illustrative Case of Chronic Pyelonephritis with Persistently Hypotonic Urine
 CHARLES R. KLEEMAN AND FRANKLIN H. EPSTEIN 488

This well studied case emphasizes several points of clinical interest in respect to pyelonephritis: absence of symptoms despite progressive destruction of the kidneys; failure of antibiotics that were effective in *in vitro* testing, and the value of combinations of antibiotics; unexplained hemolytic anemia and splenomegaly; the excretion of hypotonic urine and failure to respond to antidiuretic hormone.

- Adenocarcinoma Occurring in Regional Jejunitis
 PETER KORNFELD, LEON GINZBURG AND DAVID ADLERSBERG 493

Having observed two cases of the rather rare jejunal adenocarcinoma in regional jejunitis, apparently arising from pseudopolyps, the authors properly raise the question whether or not carcinomatous degeneration should not be considered an occasional complication of granulomatous jejunitis.

- Aplastic Anemia Fourteen Years Following Administration of Thorotrast
 GEORGE W. DUANE 499

It is impossible to establish that the aplastic anemia of this patient can be definitely ascribed to thorotrast but it would be wise to consider this possibility in patients with aplastic anemia of undetermined cause.

- "Periodic Fever." Occurrence in Five Generations
 BERTHA A. BOURONCLE AND CHARLES A. DOAN 502

The concept of periodic disease properly is viewed with skepticism by many, because the diagnosis has been indiscriminately applied by some to any disease with periodic recurrence of fever, a meaningless application. There is, however, a group of one or more disorders of unknown etiology in which the descriptive term may be used with justification, at least until the pathogenesis is elucidated. The family herein described serves as an interesting example.

Advertising Index on Page 112

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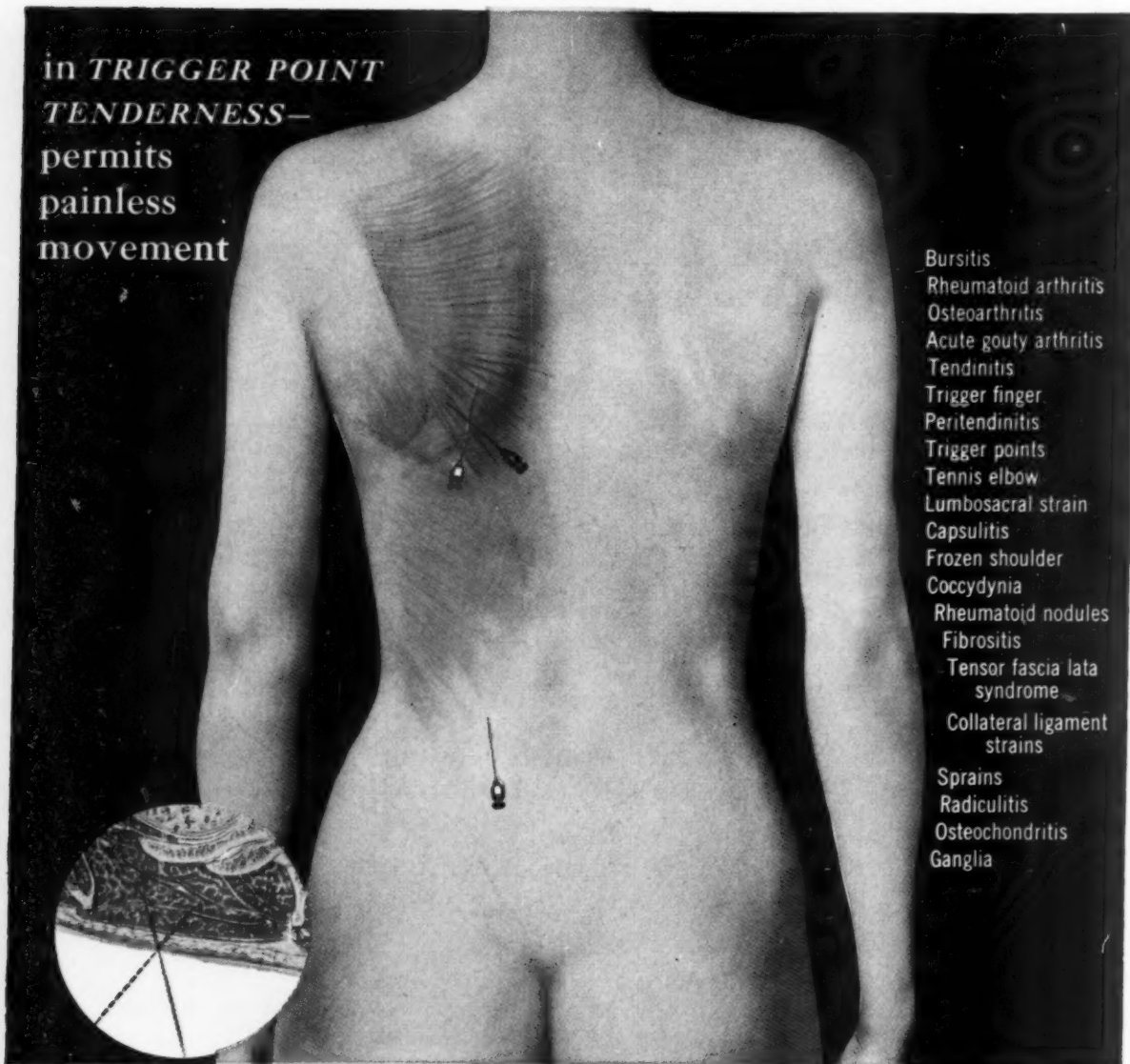
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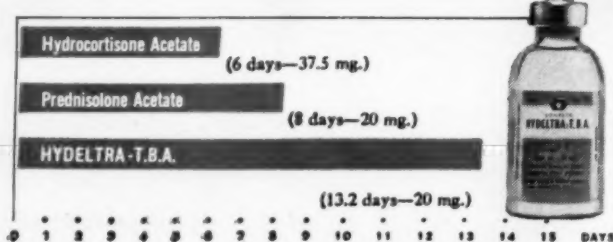
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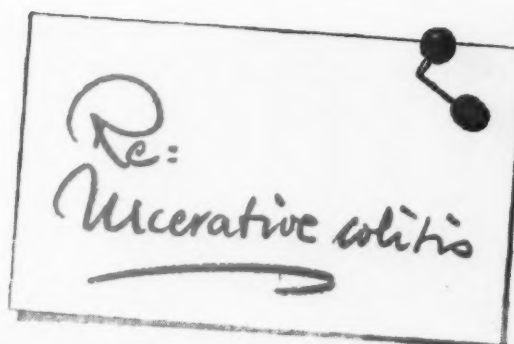
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2. BARGEN, J. A. and KENNEDY, R. L. J.: "Chronic Ulcerative Colitis in Children", *Postgrad. Med.* 17: 127 (Feb.) 1955.
3. MORRISON, L. M.: "Response of Ulcerative Colitis to Therapy with Salicylazosulfapyridine", *J. A. M. A.* 151: 366 (Jan. 31) 1953.

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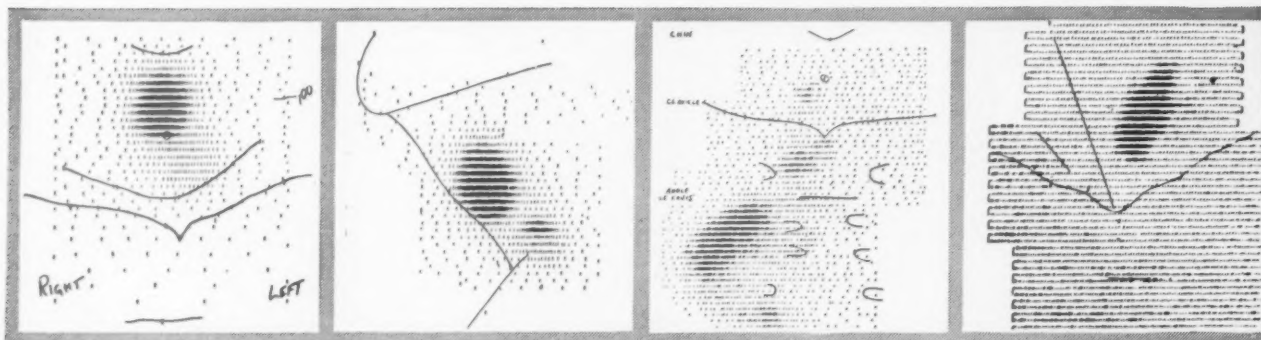


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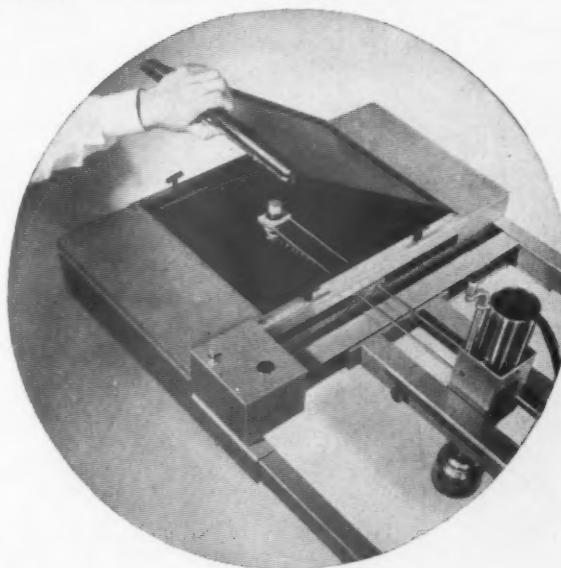
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Reference: David E. Kuhl, R. H. Chamberlain, John Hale and R. O. Gorson: A High-Contrast Photographic Recorder for Scintillation Counter Scanning. Radiology, pgs. 730-739, May, 1956.

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CLISTIN dosage forms:
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1. Johnson, H. J., Jr.: Am. Pract. & Digest.
Treat. 5:862 (Nov.) 1954.
2. Beale, H. D.; Rawling, F. F. A., and
Figley, K. D.: J. Allergy 25:521 (Nov.) 1954.

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A "...potent antihistaminic drug with only weak
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children as a serious disease,
one that may involve the
renal parenchyma and produce
renal failure in adult life.”¹*

"an effective urinary antibacterial agent in children."²

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brand of nitrofurantoin

In children, since "chronic urinary infection is generally the sequel of inadequately treated acute infection,"³ prompt and adequate therapy with FURADANTIN can prevent irreparable renal damage. FURADANTIN also "has been a safe and effective therapeutic and prophylactic drug for chronic urinary tract infection. . . . We feel the drug should be continued prophylactically for a minimum of several months after the urine has been sterilized."¹

FURADANTIN has "yielded a number of striking results in clearing up resistant infections [in children] particularly with *A. aerogenes*, *Pseudomonas aeruginosa*, and a few cases of *B. proteus*. It is generally well tolerated in the recommended dosage schedule."⁴

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In addition to unexcelled effectiveness against a wide range of gram-positive and gram-negative bacteria, FURADANTIN has a wide margin of safety. Well tolerated, FURADANTIN has proven nontoxic to kidneys, liver and blood-forming organs. No cases of monilial superinfection, crystalluria, or staphylococcic enteritis have ever been reported. In 6 years of extensive use, development of bacterial resistance remains negligible.

AVERAGE FURADANTIN DOSAGE

FURADANTIN ORAL SUSPENSION (25 mg. per 5 cc. tsp.): Average daily dose for children between 15 and 75 lbs., using 5 cc. teaspoon, is given below. Administered 4 times daily with food or milk, it is readily miscible with water, infants' formulae, milk or fruit juices.

15-24 lbs. (7-10 Kg.)	25-49 lbs. (11-22 Kg.)	50-74 lbs. (23-33 Kg.)	75 lbs. (34 Kg.)
½ teaspoonful q.i.d.	1 teaspoonful q.i.d.	2 teaspoonfuls q.i.d.	3 teaspoonfuls q.i.d.

Supplied: Bottle of 60 cc.

FURADANTIN TABLETS: Average dose for children is 5 to 7 mg. per Kg. (2.3 to 3.2 mg. per lb.) in 4 divided doses daily.

Supplied: Tablets of 50 mg. and 100 mg., bottles of 25 and 100.

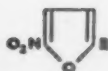
NOW for hospitalized patients, for severe urinary tract infections when peroral administration of FURADANTIN is not feasible and for serious infections as septicemia (bacteremia) when the bacterium is sensitive.

NEW, LIFESAVING FURADANTIN Intravenous Solution

REFERENCES: 1. Marshall, M., Jr., and Johnson, S. H., III.: *J. Urol.*, Balt. 76:123, 1956. 2. Johnson, S. H., III, and Marshall, M. Jr.: *A. M. A. Am. J. Dis. Child.* 89:199, 1955. 3. Campbell, M. F.: *Modern Med.* 24:85, 1956. 4. Engel, W. J.: *Med. Clin. N. America*, p. 965 (July) 1955. 5. Carroll, G.: *Pediat. Clin. N. America*, p. 781 (Aug.) 1955.

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Patients whose digestive tracts must be pampered with bland, restricted-fiber, semisolid or other limited menus, must obtain their daily nutrition from easily digested, easily assimilated foods offering high nutrient value.

Oatmeal-and-milk (whole or skim) is a food of choice in all such diets—for several reasons—and not only for breakfast: its soft particulate texture...its appealing taste...its almost complete digestibility...its rich supply of protein...and its B vitamins and minerals. Even such individualized diets as low purine, low fat, low salt, and many others give broad recognition to oatmeal because it provides high nutritional value without interfering with most dietary restrictions.

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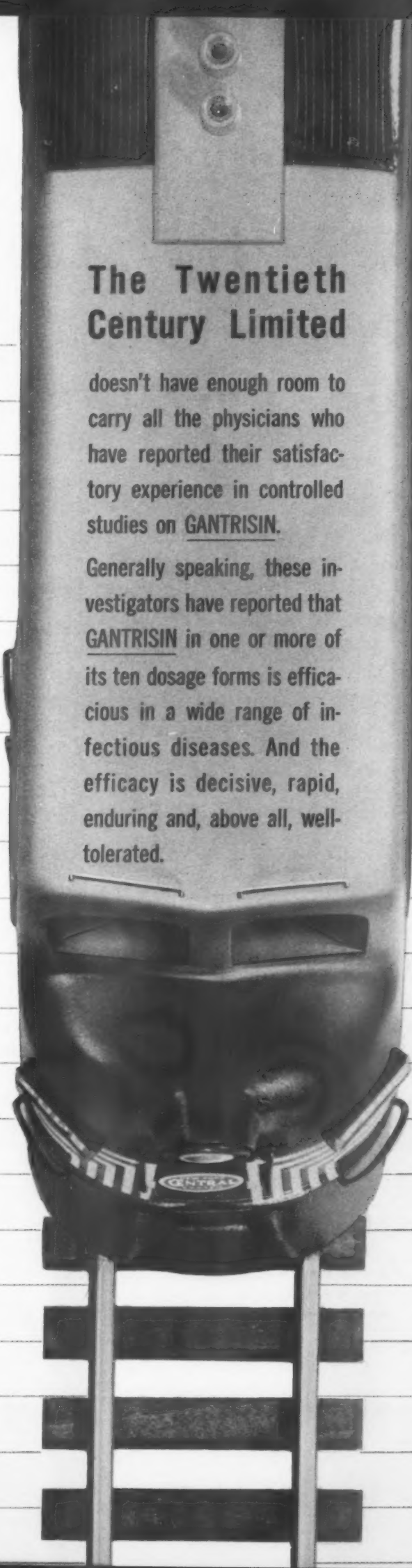
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Azo Gantrisin is an antibacterial-analgesic agent specifically designed for treatment of urinary tract infections. The high plasma and urine levels of Gantrisin act systemically and locally to clear both descending and ascending infections. Painful burning, urgency and nocturia are relieved — often within 2 hours — by the analgesic action of phenylazo-diamino-pyridine HCl upon the mucosa of the lower urinary tract.

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For antibacterial therapy and local pain relief in urinary tract infections; prevention of infection after cystoscopy, catheterization and other instrumentation. Also useful after urologic surgery.

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Wide antibacterial spectrum . . . high plasma levels . . . high urine levels . . . high solubility (even in acid urine) . . . no need for alkalies . . . no likelihood of renal blocking . . . local pain relief.

DOSAGE:

Adults (and children over 100 lbs) — 2 tablets, q.i.d.
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Caution: The usual precautions in sulfonamide therapy should be observed. Because Azo Gantrisin contains phenylazo-diamino-pyridine HCl, it is contraindicated in glomerular nephritis, pyelonephritis of pregnancy with gastrointestinal symptoms, severe hepatitis and uremia. In such cases, Gantrisin should be used alone.

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1. LaBarbera, J. F.: *Med. Rec. & Ann.* 50:242, 1956.

2. Ledbetter, P. V., and Morrow, E. J.: *J. Am. Geriatrics Soc.* 3:172 (March) 1955. 3. Wilkins, R. W.: *Am. J. Med.* 17:703 (Nov.) 1954.

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1. Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

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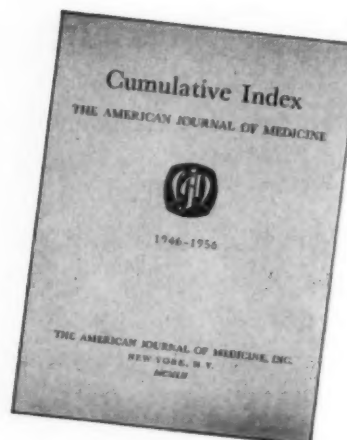
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Serpasil relieves drink-inducing tension

Long-term therapy with oral Serpasil helps the alcoholic "stay on
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Serpasil generally controls delirium tremens within 24 hours.

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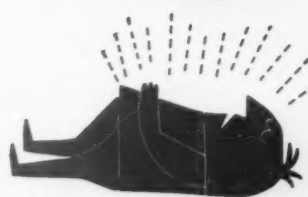
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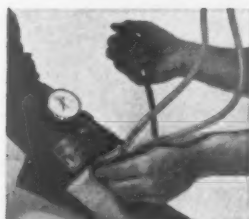
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Propenpyridamine Maleate	12.5 mg.
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Used alone or as background to more potent agents, parenteral Serpasil lowers acutely elevated blood pressure promptly and safely.

R 2.5 mg. (1 ml.) intramuscularly. Repeat every 8 to 24 hours as necessary.



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Parenteral Serpasil subdues violently agitated psychotic patients, renders them amenable to "quiet" hospitalization.

R 5 mg. intramuscularly followed, if necessary, by another 5-mg. intramuscular dose in 90 minutes.

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Finnerty, F. A., Jr., and Sites, J. G.: *Am. J. M. Sc.* 229:379 (April) 1955.

in hypertension "Serpasil alone is effective in about 70 percent of cases with mild or moderate hypertension and free of virtually any serious side effects."

Coan, J. P., McAlpine, J. C., and Boone, J. A.: *J. South Carolina M. A.* 51:417 (Dec.) 1955.

in tachycardia "Reserpine [Serpasil] was found useful in relieving the tachycardia and emotional symptoms associated with cardiac arrhythmias, thyrotoxicosis, neurocirculatory asthenia, and even coronary heart disease."

Halprin, H.: *J. M. Soc. New Jersey* 52:616 (Dec.) 1955.

in hypertensive crises "...reserpine [Serpasil] administered intramuscularly appears to be [a] treatment of choice for hypertensive crises."

Griffin, R. W., Stover, J. W., and Ford, R. V.: *New England J. Med.* 254:593 (March 29) 1956.

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Greenfield, A. R.: *Am. Pract. & Digest Treat.* 7:241 (Feb.) 1956.

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Ayd, F. J., Jr.: *The Pharmacologic Management of Everyday Psychiatric Problems* (A Scientific Exhibit). Presented at the Clinical Meeting of the American Medical Association, Boston, Mass., Nov. 29-Dec. 2, 1955.

in premenstrual tension "It was noted that this drug [Serpasil] had a quieting... effect in most instances of premenstrual tension..."

Greenblatt, R. B.: *Ann. New York Acad. Sc.* 59:133 (April 30) 1954.

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Lowsley, O. S., and Kirwin, T. J.: *Clinical Urology*, ed. 3, Baltimore, Williams & Wilkins Company, 1956, vol. 2, p. 975.

"Despite the fact that alkali was not given and no attempt was made to force fluids, [Gantrisin] did not cause the formation of concretions and there was no decrease in urine output."

Carroll, G.; Allen, H. N., and Flynn, H.: *J.A.M.A.* 142:85 (Jan. 14) 1950.

"No serious reactions due to [Gantrisin] were observed in approximately 23,000 courses of the drug."

Yow, E. M.: *Am. Pract. & Digest Treat.* 4:521 (Aug.) 1953.

"[Gantrisin] is well absorbed . . . and possesses the advantage of marked solubility in the normal pH range of urine, thus eliminating the need for alkali administration and maintenance of a high fluid intake."

Daeschner, C. W.; Clark, J. L., and Yow, E. M.: *J. Pediat.* 50:531 (May) 1957.

"Advantages of [Gantrisin] are that adjuvant alkali therapy is not mandatory, fluids need not be forced, and patients with impaired renal function can be treated with little danger of further injury to the kidney."


Goodman, L. S., and Gilman, A.: *Pharmacologic Basis of Therapeutics*, ed. 2, New York, Macmillan Company, 1955, p. 1316.

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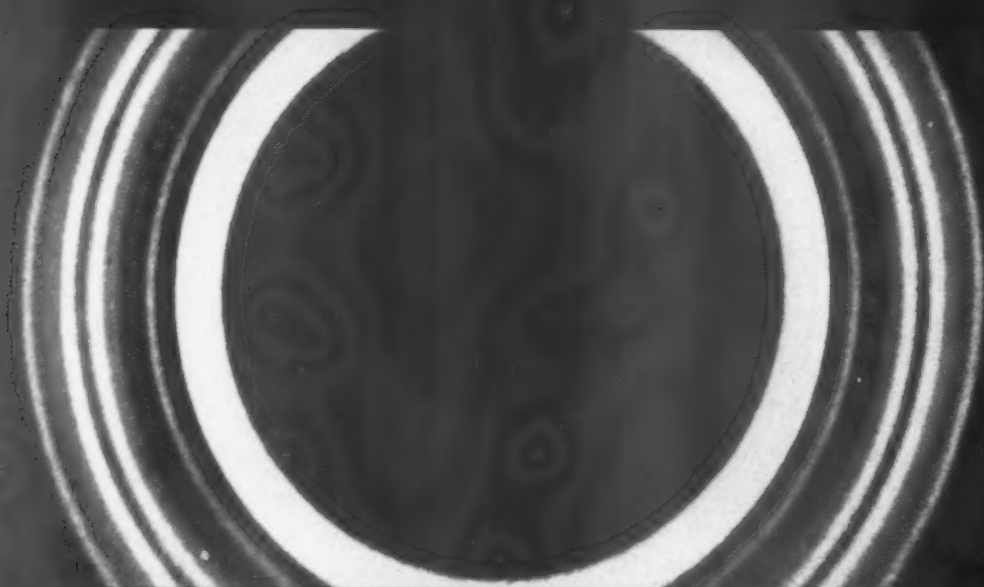


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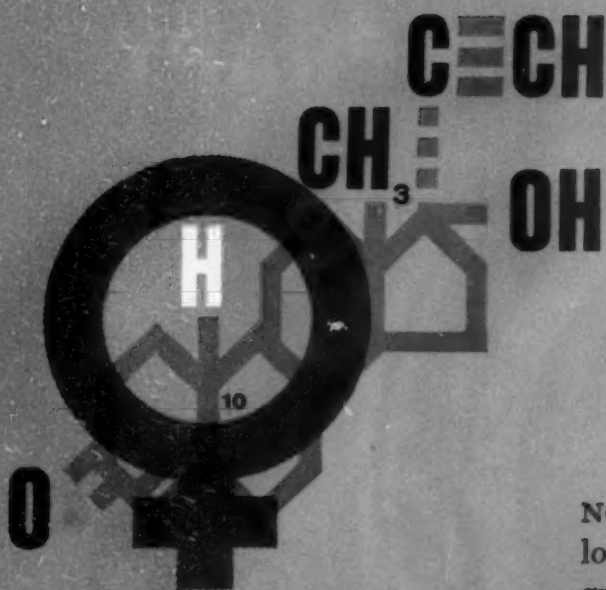
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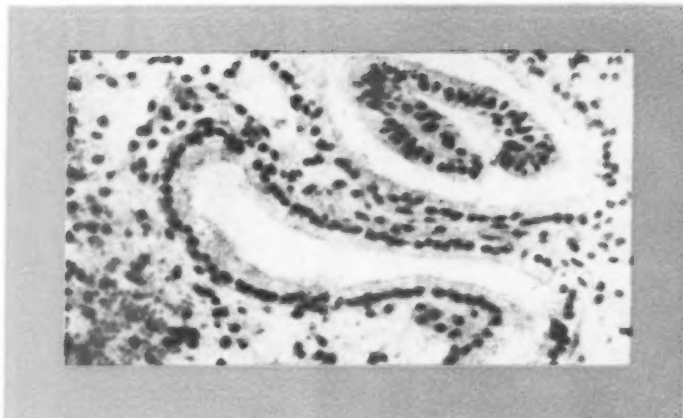


REFERENCES: (1) Hertz, R.; Tullner, W., & Raffelt, E.: *Endocrinology* 54:228, 1954. (2) Greenblatt, R. B.: *J. Clin. Endocrinol.* 16:869, 1956. (3) Hertz, R.; Waite, J. H., & Thomas, L. B.: *Proc. Soc. Exper. Biol. & Med.* 91:418, 1956. (4) Tyler, E. T.: *J. Clin. Endocrinol.* 15:881, 1955. (5) Greenblatt, R. B., & Clark, S. L.: *M. Clin. North America*, Philadelphia, W. B. Saunders Co. (Mar.) 1957, p. 587.

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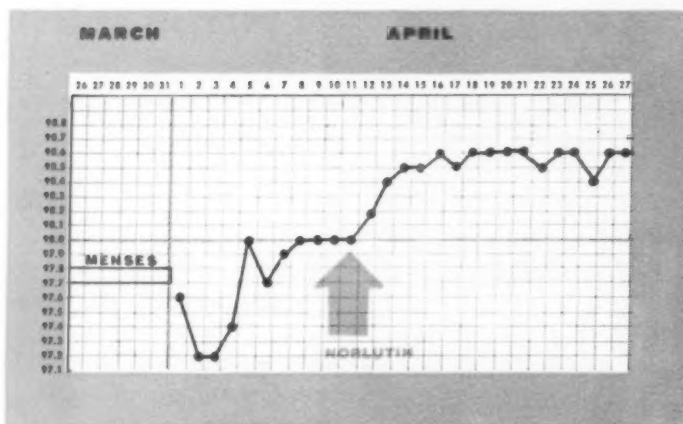
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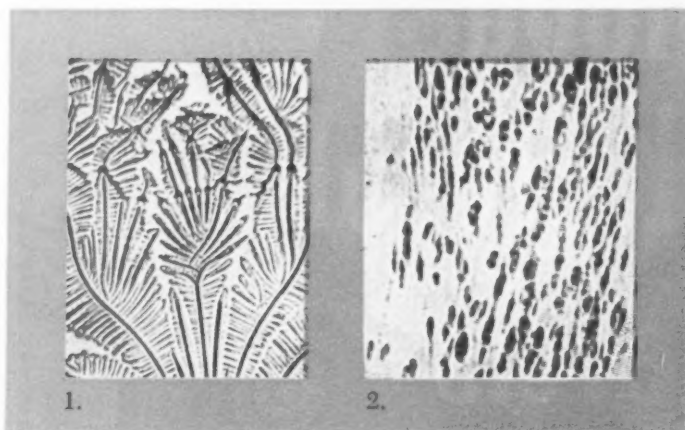


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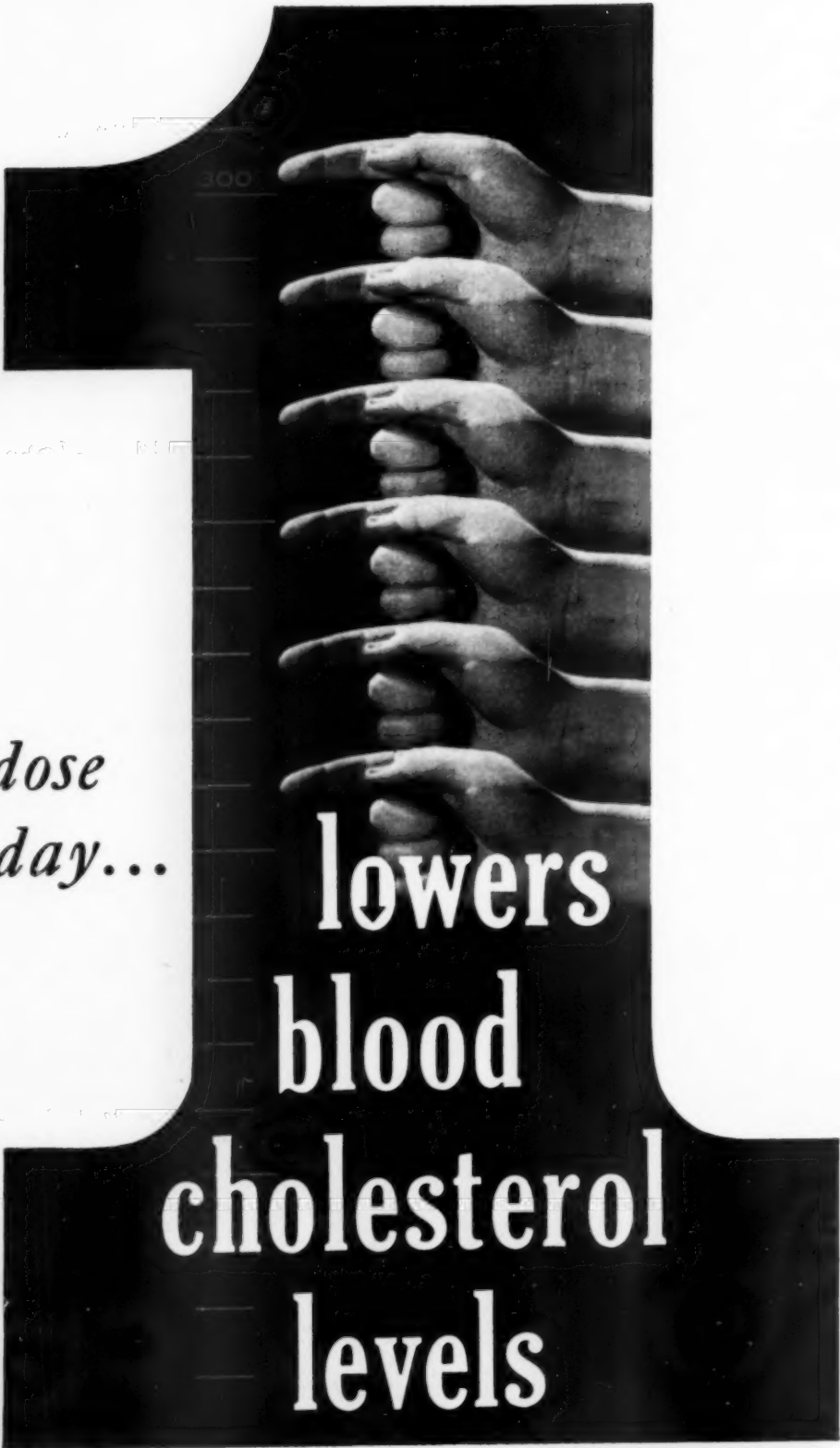
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Each tablespoonful of emulsion contains:

Linoleic acid.....	6.8 Gm.
Vitamin B ₆	0.6 mg.
Mixed tocopherols (Vitamin E)	11.5 mg.

(sodium benzoate as preservative)

Arcofac is effective in small doses
and is reasonable in cost
to the patient



**THE ARMOUR
LABORATORIES**

A DIVISION OF ARMOUR AND COMPANY
KANKAKEE, ILLINOIS



Arcofac

Armour...Cholesterol Lowering...Factor

A PLEASANT SURPRISE IN



PRENATAL SUPPLEMENTATION NEW FILIBON*

PRENATAL CAPSULES LEDERLE

More agreeable, more effective nutritional support for your pregnant and lactating patients—at no extra cost—new FILIBON offers these welcome improvements:

NEW *less irritating source of iron—ferrous fumarate—avoids gastric upset*

NEW *non-inhibitory intrinsic factor—provides greater absorption of B₁₂ to meet increased requirements*

NEW *more comprehensive formulation—includes ample amounts of phosphorus-free calcium, plus Vitamins B₆ and K, and important minerals and trace elements*

NEW *Reminder Jar—designed for the dining table, so her vitamins can't be forgotten. Re-usable later for diaper pins or cotton.*



FILIBON* Prenatal Supplement

Each capsule contains:

Vitamin A	4,000 U. S. P. Units	Iron (as Fumarate)	30 mg.
Vitamin D	400 U. S. P. Units	Intrinsic Factor	5 mg.
Thiamine Mononitrate (B ₁)	3 mg.	Fluorine (as CaF ₂)	0.015 mg.
Pyridoxine (B ₆)	1 mg.	Copper (as CuO)	0.15 mg.
Niacinamide	10 mg.	Iodine (as KI)	0.01 mg.
Riboflavin (B ₂)	2 mg.	Potassium (as K ₂ SO ₄)	0.835 mg.
Vitamin B ₁₂	2 mcgm.	Manganese (as MnO ₂)	0.05 mg.
Ascorbic Acid (C)	50 mg.	Magnesium (as MgO)	0.15 mg.
Vitamin K (Menadione)	0.5 mg.	Molybdenum	
Folic Acid	1 mg.	(as Na ₂ MoO ₄ •2H ₂ O)	0.025 mg.
Ferrous Fumarate	90 mg.	Zinc (as ZnO)	0.085 mg.
		Calcium Carbonate	575 mg.

Dosage: one or more capsules daily

Supplied: attractive, re-usable bottles of 100 capsules

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LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK



specific vitamin
therapy from
the express wagon
set to the juke box
Jills and Joes

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THERAGRAN junior

SQUIBB VITAMINS FOR THERAPY



now... the time-tested, clinically proved
Theragran formula especially adapted and
encapsulated to meet your needs for vitamin
therapy in children and adolescents

*Each small, easy-to-take
Theragran Junior capsule supplies:*

Vitamin A.....	5000 U.S.P. units
Vitamin D	1000 U.S.P. units
Thiamine mononitrate	5 mg.
Riboflavin	5 mg.
Niacinamide	30 mg.
Ascorbic acid	100 mg.
Pyridoxine hydrochloride	2 mg.
d-Calcium pantothenate	3 mg.
Vitamin B ₁₂ activity concentrate	10 mcg.

DOSAGE:

1 or 2 capsules daily, or as directed by the physician.

SUPPLY:

Bottles of 30 and 100 capsules.

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family:*

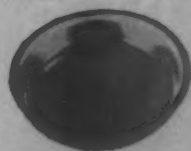
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contains: a hydrophilic plantago derivative to help form soft, cohesive stools; thiamine, often needed to improve peristaltic function.

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For Daytime Tranquillity

non-barbiturate sedative

- Quick acting
- Rapidly eliminated
- Free from side effects

Dose: 1 BROMURAL tablet several times a day.

Try 1 Bromural tablet with an aspirin for quicker relief of neuralgic pain and headache, discomfort and the aches of simple colds — better than aspirin alone.

Each BROMURAL tablet bears the mark ⊕ of the originator.

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"promotes
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1. Spiesman, M. G. and Malow, L.: Amer. J. Proctology, June 1956.

2 NEW CONVENIENT ORAL FORMS

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TETRACYCLINE BUFFERED WITH PHOSPHATE

SYRUP

Orange Flavor. Each teaspoonful (5 cc.) contains 125 mg. of tetracycline, phosphate-buffered. Bottles of 2 and 16 fl. oz.

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Orange Flavor. Each cc. contains 100 mg. of tetracycline, phosphate-buffered. (Approx. 5 mg. per drop). 10 cc. plastic dropper-type bottle.

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aqueous, freely miscible,
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← anti-stress aid →
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the most effective treatment known for dandruff

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simple, agreeable to use

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a medical answer to a medical problem

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*potent antianemia therapy
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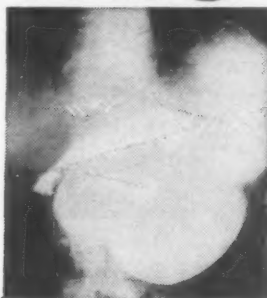
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THE AMERICAN JOURNAL OF CLINICAL NUTRITION

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when anxiety and tension "erupts" in the G. I. tract...

IN GASTRIC ULCER



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Meprobamate with PATHILON® Lederle

Combines Meprobamate (400 mg.) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of gastric ulcer — without fear of barbiturate loginess, hangover or habituation . . . with PATHILON (25 mg.) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime.


Supplied: Bottles of 100, 1,000.



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for significant
reduction of elevated
serum cholesterol

new **LINO**

linoleic acid (essential unsaturated fatty acid) and pyridoxine HCl

two factors recommended as aids in the
management and prevention of atherosclerosis

linoleic acid — essential unsaturated fatty acid — to
help restore and maintain the proper ratio between
saturated and unsaturated fat in the diet

pyridoxine — essential for the utilization of linoleic
acid in the body

PFIZER LABORATORIES, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.



Hypercholesterolemia and Atherosclerosis

Although the exact etiology of atherosclerosis is not known, there is overwhelming and mounting evidence implicating elevated serum cholesterol in the pathological processes leading to the formation of atheromatous lesions.^{1,2} In a recent study of 898 men, 45 to 62 years of age, approximately 49 per cent initially showed serum cholesterol levels of 225 mg. per cent, or higher. Hypercholesterolemia was strongly associated with the development of new arteriosclerotic heart disease in this age group during four years of follow-up study.³

Statistically, hypercholesterolemia has regularly been shown to have a positive correlation with atherosclerosis.⁴ Reduction of elevated serum cholesterol levels appears to be warranted, therefore, in all patients with hypercholesterolemia.

References: 1. Keys, A.: Am. J. Pub. Health 43:1399 (Nov.) 1953. 2. Gutman, A. B.: Am. J. Med. 14:1 (Jan.) 1953. 3. Dawber, T. R.; Moore, F. E., and Mann, G. V.: Am. J. Pub. Health 47:4 (April) 1957. 4. Keys, A.: Proceedings, Conference on Atherosclerosis and Coronary Heart Disease, New York Heart Association, Inc., New York, Jan. 15, 1957, p. 20.

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Low in calories; pleasantly orange flavored; no taste fatigue during long-term therapy

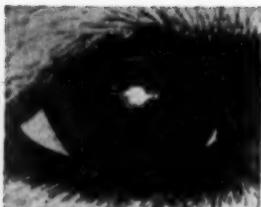
Useful *prophylactically* or *therapeutically* in patients who either show elevation of serum cholesterol or fall into one or more of the following clinical categories: male patients with precordial pain; overweight middle-aged patients of both

sexes; patients with visibly tortuous superficial arteries; patients with elevated blood pressure

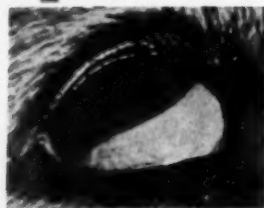
Dosage: 1 tablespoonful 3 times daily before meals, alone or mixed with liquid or solid foods

Supply: Bottles of 1 pint, each 15 cc. tablespoonful containing 4.5 grams of linoleic acid, 5 mg. of pyridoxine hydrochloride, and 20 mg. of mixed tocopherols as an antioxidant

^{*}TRADEMARK

in  nictitating membrane of unanesthetized dog before administration of Ecolid

**severe
hypertension
dramatic
response**



membrane of same dog eight hours after administration of 2 mg./kg. Ecolid shows dramatic ganglionic blocking effect¹

Potent, orally and parenterally effective ganglionic blocking agent,

Ecolid[®] has dramatically reversed the course of severe hypertension in some patients, and has prolonged their lives. It

produces a longer lasting, smoother and more consistent and predictable

response than either pentolinium or hexamethonium. However, as

with all ganglionic blocking agents, the patient must be carefully

managed. Before instituting treatment with **Ecolid** it is

advised that the physician be thoroughly familiar with this drug's effects

as well as side effects. Complete literature may be obtained from the

Medical Service Division, CIBA, Summit, New Jersey.

SUPPLIED: TABLETS (Rotocotes), 10 mg. (orange), 25 mg. (ivory) and 50 mg. (pink). PARENTERAL SOLUTION: Ampuls, 1 ml., 5 mg. per ml.

ECOLID[®] chloride (chlorisondamine chloride CIBA)

ROTOCOTES[®] (compressed, dry-coated tablets CIBA)

1. Plummer, A.J., Trapold, J.H., Schneider, J.A., Maxwell, R.A., and Earl, A.E.: J. Pharmacol. & Exper. Therap. **115**:172 (Oct.) 1955.

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SUMMIT, N. J.

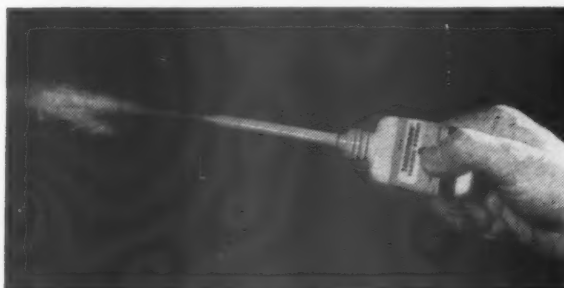
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"TWO STEP" TREATMENT

You can assure thorough eradication of trichomonads as well as rapid relief from itching and burning with this *combined* therapy:

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Control in your office—to minimize patient failures: TRICOFURON VAGINAL POWDER (0.1% Furoxone®, brand of furazolidone, in an acidic powder base). Applied by the physician at least once a week, except during menstruation.

NEW for easy insufflation:
plastic "puffer" bottle of 15 Gm.,
supplied with 3 sanitary disposable tips.
Also available: glass bottle of 30 Gm.

STEP 2



Continued *home* use to maintain trichomonacidal action: TRICOFURON VAGINAL SUPPOSITORIES (0.25% Furoxone in a water-miscible base).

Employed by the patient each morning and night the first week and each night thereafter—through one cycle, including the important menstrual days.

Box of 12, each hermetically sealed in green foil.



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FOR THE ENTIRE RANGE OF RHEUMATIC-ARTHRITIC
DISORDERS—from the mildest
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many patients with MILD involvement can be effectively
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'MEPROLONE'

many patients with MODERATELY SEVERE involvement
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MULTIPLE COMPRESSED TABLETS

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and NOW for patients with
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The first meproamate-prednisolone therapy

the one antirheumatic, antiarthritic that
simultaneously relieves: (1) muscle spasm
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SUPPLIED: Multiple Compressed Tablets
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5.0 mg. prednisolone, 400 mg. meproba-
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ALMOST every physician makes use of nutritional principles and practice in his daily work. This is the point of view underlying The American Journal of Clinical Nutrition which conceives of nutrition as an adjunct in the total care of every patient. Cutting across arbitrary boundaries of specialties, nutrition is used by internist, surgeon, pediatrician and obstetrician alike. It has been called "the cornerstone of preventive medicine, the handmaiden of curative medicine, and the responsibility of every physician."

As part of our objective of integrating modern concepts of nutrition into clinical practice, The American Journal of Clinical

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Combines Meprobamate (400 mg.) the most widely prescribed tranquilizer . . . helps control the "emotional overlay" of duodenal ulcer — without fear of barbiturate loginess, hangover or habituation . . . with PATHILON (25 mg.) the anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of many G.I. disorders.

Dosage: 1 tablet t.i.d. at mealtime. 2 tablets at bedtime.

Supplied: Bottles of 100, 1,000.



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Predictable hypotensive effect—orally

INVERSINE®

MECAMYLAMINE HYDROCHLORIDE

INVERSINE—a secondary amine, different from all other ganglionic blocking agents—has many clinical advantages: **1.** Gives reproducible effects. **2.** Is most potent of all oral ganglionic blockers. **3.** Provides smooth and predictable response. **4.** Is completely absorbed. **5.** Onset of action is gradual. **6.** Small oral dose gives desired hypotensive effect. **7.** Is effective even in patients refractory to other ganglionic blockers.

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Obedrin® To help the overweight patient establish correct eating patterns.

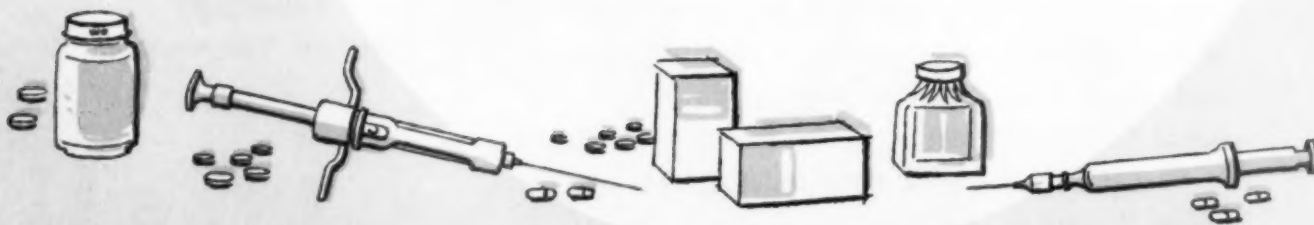
Homagenets® The only solid homogenized vitamins. Three formulas: prenatal, pediatric, and therapeutic.

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Salcort® Cortisone-salicylate therapy, without undesirable side reactions.

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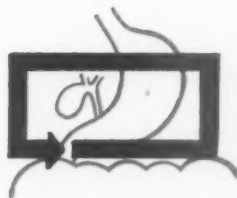
*for pain \rightleftharpoons spasm
of the upper G.I. tract*

capsule

DACTIL®

Brand of Piperidolate HCl

*visceral eutonic
relieves gastroduodenal
and biliary pain \rightleftharpoons spasm
—usually in 10 minutes*



for peptic ulcer

tablet

PIPTAL®

Brand of Pipenzolate
Methylbromide

*cholinolytic
normalizes motility
and secretion; prolongs
remissions, curbs
recurrences*



*for generalized
G.I. disorders*

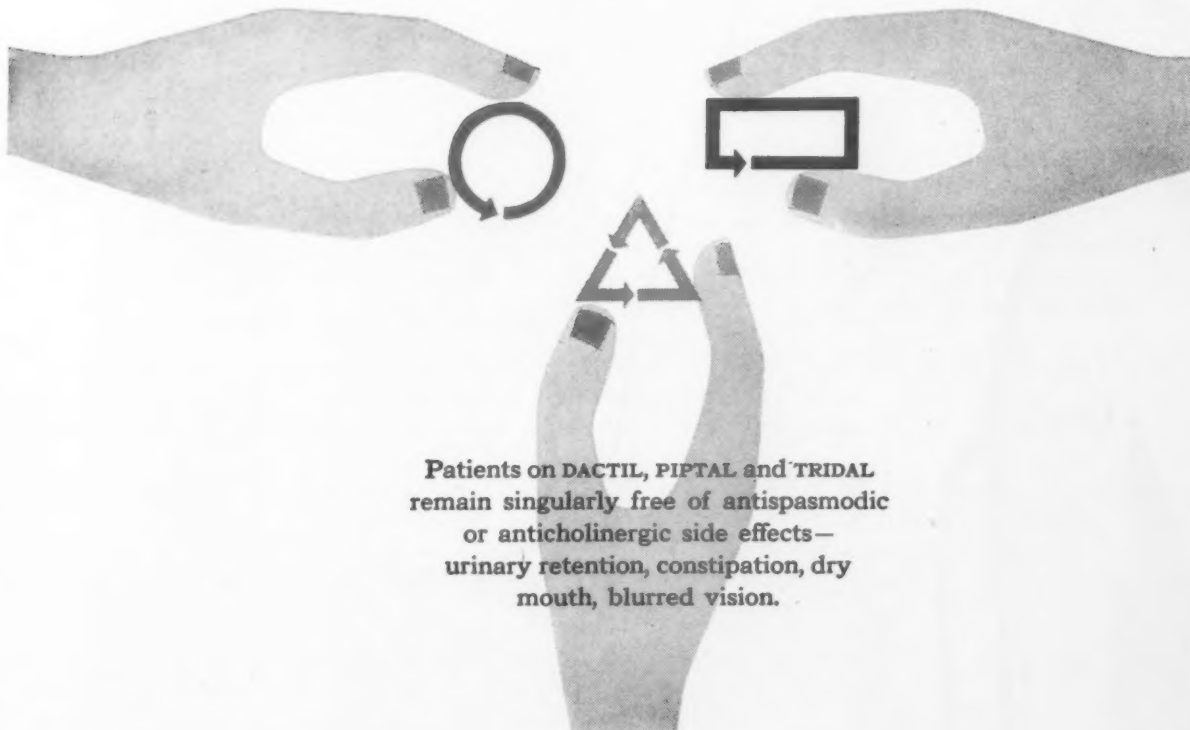
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TRIDAL®

(DACTIL+PIPTAL—in one tablet)

*rapid, prolonged relief
throughout
the G.I. tract*

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**Patients on DACTIL, PIPTAL and TRIDAL
remain singularly free of antispasmodic
or anticholinergic side effects—
urinary retention, constipation, dry
mouth, blurred vision.**



Now, from the safflower
...an important, new aid
for reduction
of elevated cholesterol
blood levels

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TRADEMARK

(ABBOTT'S SAFFLOWER OIL EMULSION)



PALATABLE, NEW EMULSION
OFFERS THE HIGHEST PERCENTAGE
OF UNSATURATED FATTY ACIDS
OF ALL VEGETABLE OILS



Over recent years, the study of atherosclerosis has strongly suggested that its control may be aided through the correction of hypercholesteremia. It has been repeatedly observed, further, that the substitution of highly unsaturated fats for saturated fats reduces elevated cholesterol blood levels in certain individuals.

With the highest percentage of unsaturated fats of all edible vegetable oils, Abbott's new safflower oil emulsion, SAFF, is thus indicated in the management of hypercholesteremia. Significantly, safflower oil, while representing a uniquely concentrated natural source of linoleic acid, contains the *lowest* percentage of saturated fatty acids. The following table shows the relation between fatty acid composition and biological activity in a number of food fats:

	Linoleic Acid	Other Polyenic Acids	Saturated Acids	Biological* Activity
Safflower oil	74.5%	—	6.6%	78.8%
Soybean oil	53.3%	7.8%	13.2%	62.4%
Corn oil	56 %	—	13 %	—
Cottonseed oil	49.6%	1.3%	26 %	48.5%
Sesame oil	41 %	—	13 %	28.2%
Linseed oil	12.5%	52.1%	9.6%	11.9%
Olive oil	12 %	—	12 %	—
Lard	5.6%	1.3%	43 %	6.9%
Tallow (beef)	0.9%	1 %	53 %	1.5%
Butter	2 %	1.7%	47 %	1.1%
Margarine	5.8%	—	23 %	—
Coconut oil	1.9%	—	82 %	1.1%

*Relative potency for curing essential fatty acid deficiency in rats when linoleic acid is assigned a value of 100. Thomassen, H. J.: "Biological Standardization of Essential Fatty Acids", International Rev. of Vit. Res., 25:62, 1953.

In relating diet to blood cholesterol, one typical study¹ included five groups of human subjects, whose controlled diets alternated from

large percentages of unsaturated fats to identical percentages of saturated fats. Conclusions drawn were that plasma cholesterol increased with ingestion of saturated fats whereas a diet of unsaturated fats consistently *decreased* plasma cholesterol. Such studies strongly suggest that unsaturated fat can be of value in the regulating of hypercholesteremia.

Clinical and Laboratory Findings

In promoting the growth, well-being, and survival of experimental animals, safflower oil (SAFF) has proved much more effective than hydrogenated vegetable oil. Indeed, in the laboratory,² atheroma-like changes have been produced in rabbits on a purified ration containing hydrogenated vegetable oil. No such lesions resulted from the administration of comparable quantities of safflower oil.

SAFF finds ready acceptance in the management of conditions where weight-gain is desirable—such as undernutrition or convalescence. Moreover, from studies, such as those of Deuel and Reiser,³ it is evident that unsaturated fats have a special value in nutrition—one not shared by any other kind of food.

Opportunity For Immediate Study

SAFF's true worth can best be demonstrated through studies in which it is administered to patients with hypercholesteremia, including those with atherosclerosis, or those having a tendency toward it. Again, in individuals with coronary disease, the effect of controlled essential fatty acid intake on cholesterol and lipid blood levels will be of particular significance.

In many patients, substitution of SAFF for saturated fat in the diet will provide a demonstrable lowering of blood cholesterol.

With a light butterscotch flavoring, SAFF is highly palatable right from the spoon. Mixes easily with most liquids as well as with a number of foods.

SAFF's recommended dosage is five table-spoons daily. Available in one-pint-bottles.

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- REFERENCES:** 1. Beveridge, J. M. R.; Connell, W. F.; and Mayer, G. A.: "Dietary Factors Affecting the Level of Plasma Cholesterol in Humans: The Role of Fat." *Canad. J. Biochem. & Physiol.* 34:441-55, May, 1956. 2. Lambert, G. F.; Olson, R. T.; Miller, J. P., Jr.; and Frost, D. V.: *Laboratory Records, Nutrition Research, Abbott Laboratories*, 1956-57. 3. Deuel, H. J. Jr., and Reiser, R.: "The Physiology and Biochemistry of the Essential Fatty Acids." *Vitamins and Hormones*, Volume 13, pp. 29-70, 1955



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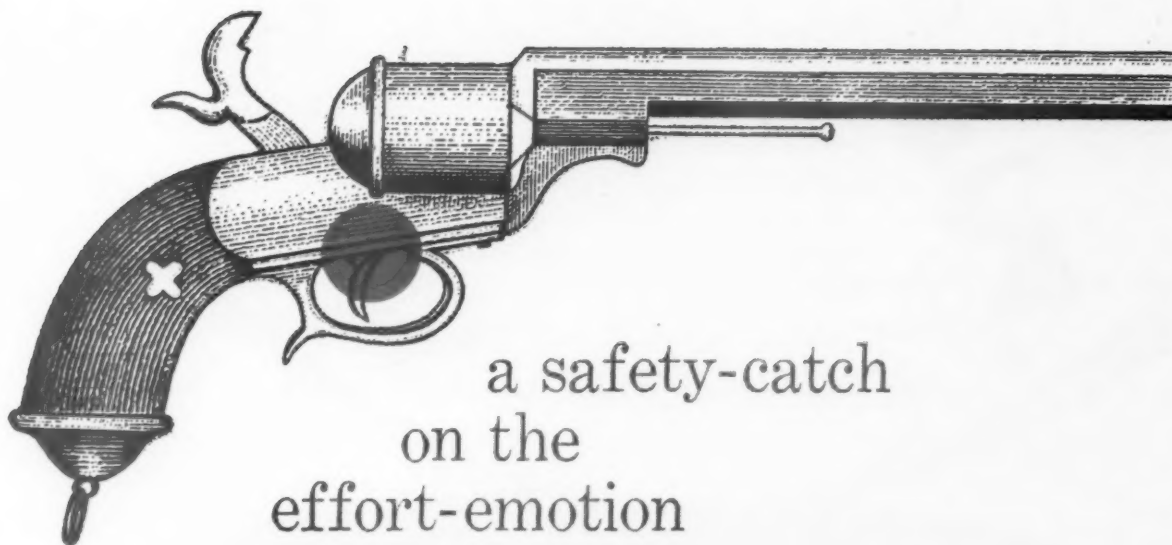
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References: (1) Deitz, G. W.: *Am. Pract. & Digest Treat.* 6:1872, 1955. (2) Russek, H. I.; Zohman, B. L.; Drumm, A. E.; Weingarten, W., and Dorset, V. J.: *Circulation* 12:169, 1955. (3) Dripps, R. D.: *J.A.M.A.* 139:148, 1949. (4) Lewis, B. I.; Lubin, R. C.; January, L. E., and Wild, J. B.: *Circulation* 14:227, 1956.

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Editorial

The Syndrome of Alveolar Hypoventilation

"As I walk round a tree, I learn that the parts still visible, those that have just disappeared and those now coming into view, are continuous and belong to the same tree."

GEORGE SANTAYANA, *"The Life of Reason"*

As long as the diagnostic armamentarium of the physician was confined to physical and x-ray examination of the chest and to bacteriologic examination of the sputum, interest in chest disease centered around anatomic and etiologic diagnosis of structural abnormalities of the lungs. The greatest yield from the use of these tools has been in the characterization of localized pulmonary disease. With the application of physiologic methods to the study of the respiration and circulation in man, the focus has widened to include generalized pulmonary diseases and the changes in body economy which they effect.

A particularly fruitful approach to the problem of diffuse pulmonary disease has been the separation of the physiologic manifestations of diverse anatomic lesions, induced by a wide variety of etiologic agents, into two broad groups: (1) disruption of the normal balance between alveolar ventilation and perfusion, and (2) impediment to the exchange of oxygen, and ultimately to carbon dioxide, between alveolar air and pulmonary capillary blood. The first group is typified by chronic obstructive pulmonary emphysema; the second is illustrated by the diseases of the pulmonary interstitium, i.e. "alveolar-capillary block." This approach has been tempered by the awareness that combinations of these two groups are common and that in far advanced disease, with marked changes in the gaseous composition of arterial blood, the physiologic bases for distinction become blurred.

Recently, a third pattern has emerged in which arterial hypoxemia and hypercapnia, of a

degree comparable to that observed in the most extensive pulmonary disease, occur in patients with normal lungs; in this instance, poor performance of the chest bellows rather than intrinsic lung disease underlies the inadequate exchange of gases between ambient air and arterial blood.

The chest bellows is the target of a ventilatory drive synthesized in the respiratory center. In the upper half of Figure 1 the respiratory center is depicted as a switchboard upon which afferent stimuli converge, and from which motor stimuli are channeled into the appropriate neuromuscular pathways to drive the chest bellows. For the sake of convenience and presumably with little sacrifice in concept, intracellular and arterial blood pH have been ignored, and the arterial blood carbon dioxide tension (P_{CO_2}) has been singled out as the dominant stimulus to ventilation.

The lungs have been deliberately omitted from this figure since their anatomic position renders them dependent on the chest bellows for their expansion. Their primary contribution to the ventilatory drive is indirect and stems from their control of the level of arterial blood P_{CO_2} ; the latter, in turn, depends on the adequacy with which alveolar ventilation exposes pulmonary capillary blood to fresh alveolar air. The representation in Figure 1 consequently emerges as a servo-mechanism in which alveolar ventilation, a by-product of the excursions of the chest wall, regulates the output of efferent ventilatory stimuli to the chest bellows by adjusting the level of arterial blood P_{CO_2} .

The arterial blood P_{CO_2} may then be con-

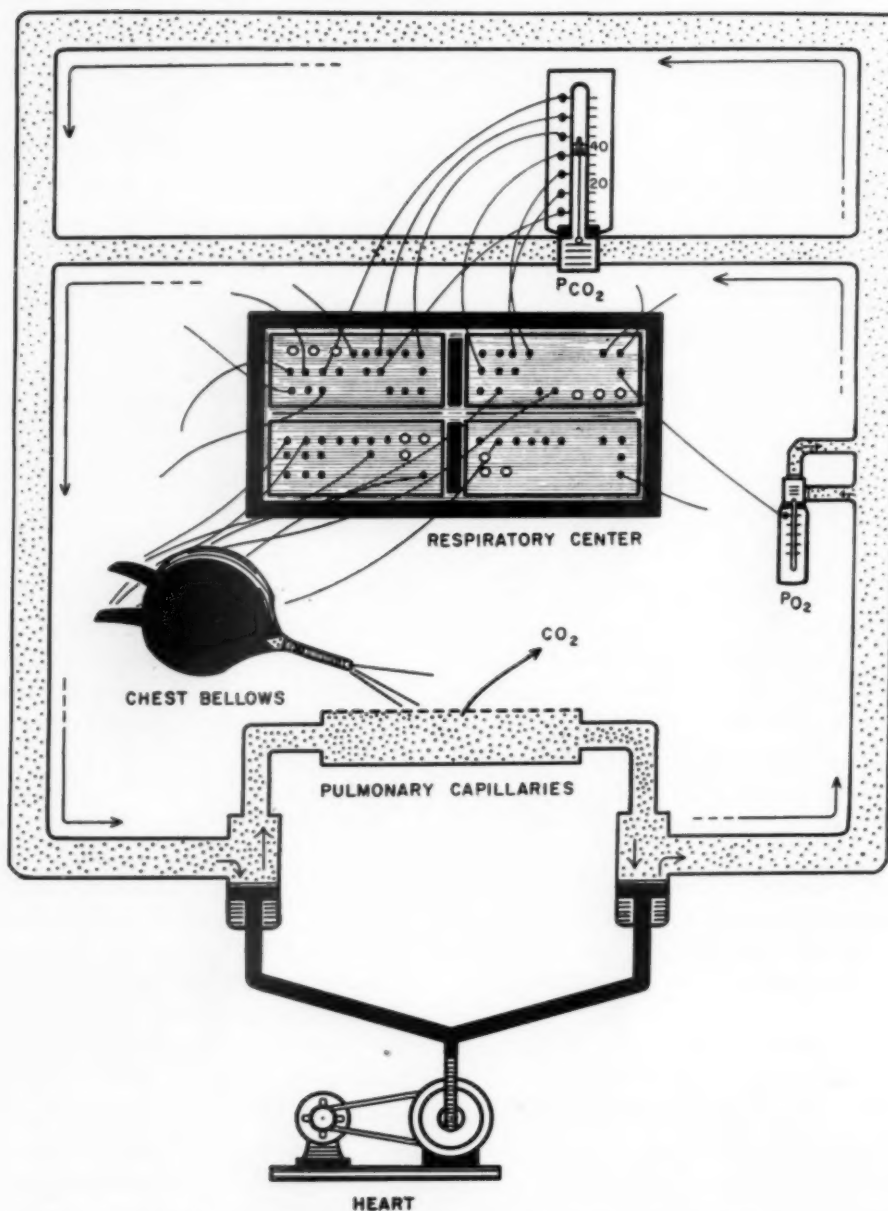


FIG. 1. Schematic representation of the regulation of ventilation.

sidered as the pivot in the regulation of ventilation. In normal subjects at sea level, its value deviates little from 40 mm. Hg, even during moderate exercise. This value reflects a delicate balance between the metabolism and alveolar ventilation of the subject; an arterial blood P_{CO_2} appreciably greater than 40 mm. Hg consequently defines alveolar hypoventilation; conversely, an arterial blood P_{CO_2} less than 40 mm. Hg defines alveolar hyperventilation.

It has been repeatedly demonstrated that in normal human subjects the alveolar P_{CO_2} is virtually identical with arterial blood P_{CO_2} . In Figure 2 is illustrated a graphic solution of the

mathematical relationship between alveolar (or arterial blood) P_{CO_2} , metabolism (\dot{V}_{O_2}) and alveolar ventilation (\dot{V}_A). The sloping line, derived for alveolar $P_{CO_2} = 40$ mm. Hg, separates the shaded zone of alveolar hypoventilation from that of hyperventilation.

Arterial hypoxemia, expressed as a decrease in oxygen tension, is an invariable concomitant of alveolar hypoventilation. However, in practice, hypoxemia is a less reliable guide to the detection of alveolar hypoventilation than is the arterial blood P_{CO_2} , since: (1) hypoxemia may occur in a variety of other conditions, (2) it is obscured when enriched oxygen mixtures are

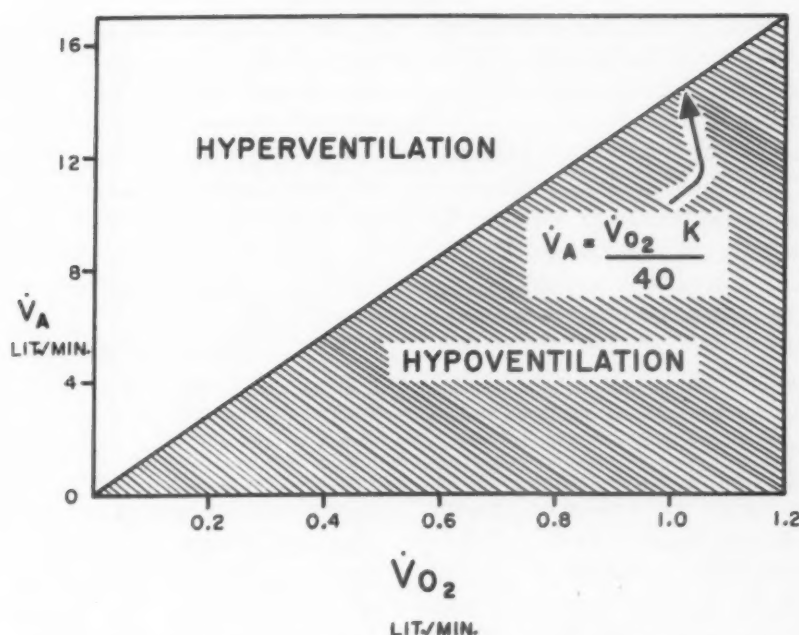


FIG. 2. Relation between alveolar ventilation (\dot{V}_A) and O_2 consumption (\dot{V}_{O_2}) in the steady state.

breathed, and (3) the estimation of arterial blood P_{O_2} at relatively normal levels of oxygenation is considerably more difficult than the estimation of alveolar and arterial blood P_{CO_2} .

Obviously, the balance between alveolar ventilation and the metabolic production of carbon dioxide must be precise in order to maintain a relatively constant arterial blood P_{CO_2} over a wide range of metabolic activity. It is also clear that barely perceptible reductions in alveolar ventilation may suffice to establish arterial hypercapnia, respiratory acidosis and arterial hypoxemia. Indeed, in the normal subject the onset of chronic alveolar hypoventilation must perforce be insidious since deliberate attempts at underventilation, such as may be accomplished by breath holding or by the application of a restrictive chest binder, are defeated by an overpowering ventilatory drive. Consequently, it is not surprising that the clinical detection of alveolar hypoventilation prior to the advent of somnolence and cyanosis is generally exceedingly difficult.

The unfavorable consequences of alveolar hypoventilation arise from the abnormalities in blood gas composition. If the carbon dioxide retention is sufficiently severe and rapid in onset, narcosis and death may occur. However, hypoxemia, rather than hypercapnia, is largely responsible for the dire consequences of alveolar hypoventilation; the deleterious effects of sys-

temic hypoxemia are exerted by imposing a circulatory burden on the right side of the heart. This circulatory overload stems from polycythemia, hypervolemia, increased cardiac output and pulmonary hypertension; that it derives from hypoxemia rather than hypercapnia is demonstrated by the strain on the right side of the heart which is often manifested by the hypoxemic, *hypocapnic* residents at high altitude.

A similar combination of carbon dioxide retention and arterial hypoxemia may occur late in the course of chronic obstructive pulmonary emphysema. It is worthy of emphasis that even though the end-point is the same—no matter how alveolar hypoventilation is produced—the pattern of evolution of these abnormalities in blood gas composition is strikingly different. Thus, in emphysema the patchy nature of the disease process is responsible for an intermediate stage of arterial hypoxemia without hypercapnia; during this stage the hyperventilation of well-perfused alveoli accomplishes, by virtue of differences in blood gas dissociation curves, an adequate output of carbon dioxide without compensating for the diminished uptake of oxygen in underventilated areas of the lung. It is only in time, as the disease progresses or as infection is superimposed, that the compensatory effect of these hyperventilated alveoli becomes ineffective and “net” alveolar hypoventilation ensues. By way of contrast, it

should be stressed that throughout the entire course of alveolar hypoventilation in patients with normal lungs, hypoxemia and hypercapnia go hand-in-hand.

As has already been pointed out, in patients with normal lungs alveolar hypoventilation is a result of insufficient ventilatory drive. In accord with the schematic representation of Figure 1, a diminution in ventilatory drive may be visualized as a consequence of derangement at any one of four general "sites": stimulus, respiratory center, neuromuscular coordination or chest bellows. Although convenient from the point of view of presentation, this approach is obviously an oversimplification since disease may simultaneously affect more than one factor in the regulation of ventilation.

Alveolar hypoventilation secondary to disturbances in neuromuscular coordination occurs as a major event in the course of poliomyelitis [1] and of myasthenia gravis. In these instances the factors responsible for alveolar hypoventilation are sufficiently clear as to warrant no further amplification.

Another basis for a diminished ventilatory drive is a deficiency in ventilatory stimuli. Such a mechanism may contribute to the transient periods of hypoventilation which characterize Cheyne-Stokes breathing.

On the other hand, a sustained state of hypoventilation due to a primary lack of a major stimulus can occur only under select circumstances because of concomitant changes in the sensitivity of the respiratory center and in the contribution of other stimuli. For example, a sustained state of hypoventilation due to a chronic deficiency of the P_{CO_2} stimulus is generally defeated by the combination of a hypoxic stimulus and a heightened sensitivity of the respiratory center to the P_{CO_2} stimulus; this type of adjustment is characteristic of residents at high altitudes. Conversely, in metabolic alkalosis the decrease in pH stimulus is apparently accompanied by a diminution in sensitivity to both the pH and P_{CO_2} stimuli [2]; this adjustment may then serve as a device to restore tissue and blood pH toward normal levels.

¹ LUKAS, D. S. and PLUM, F. Pulmonary function in patients convalescing from acute poliomyelitis with respiratory paralysis. *Am. J. Med.*, 12: 388, 1952.

² ALEXANDER, J. K., WEST, J. R., WOOD, J. A. and RICHARDS, D. W. Analysis of the respiratory response to carbon dioxide inhalation in varying clinical states of hypercapnia, anoxia and acid-base derangement. *J. Clin. Investigation*, 34: 511, 1955.

Probably the most clear-cut demonstration of the relation between alveolar hypoventilation and inadequate chemical stimulation is observed when hypoxemia, usually a minor stimulus, is completely relieved in patients with pre-existing alveolar hypoventilation and hypercapnia; in such patients, the complete relief of hypoxemia, as by the administration of pure oxygen, aggravates the alveolar hypoventilation, occasionally to the point of apnea [3].

The remainder of this discussion will be concerned with the clinical expressions of derangements at the two remaining "sites," the respiratory center and the chest bellows.

The respiratory center may conceivably suffer two general types of depression: (1) anatomic, due to strategically located lesions in the medulla, or (2) physiologic, due to changes in its chemical milieu. The first group is exemplified by the injuries of bulbar poliomyelitis and vascular thrombosis; the second is illustrated by patients with chronic carbon dioxide retention. Distinction between anatomic and physiologic derangements may be lost once carbon dioxide retention is established.

There are, indeed, few instances in which anatomic injury may be invoked with any degree of assurance. A few such patients have been reported with either a history of antecedent inflammatory disease of the central nervous system [4,5] or a mechanism for vascular thrombosis [6]. They are characterized by polycythemia, arterial hypoxemia and hypercapnia, with normal lungs and chest bellows. On testing, they fail to augment ventilation appreciably either during carbon dioxide breathing or during exercise; in striking contrast to this deficiency in *involuntary* control is the normal *voluntary* maximum ventilatory capacity. It must be stressed that the evidence for anatomic injury in these subjects remains circumstantial. However, since polycythemia *per se* is not associated

³ FISHMAN, A. P., SAMET, P. and Cournand, A. Ventilatory drive in chronic pulmonary emphysema. *Am. J. Med.*, 19: 533, 1955.

⁴ Ratto, O., BRISCOE, W. A., MORTON, J. W. and COMROE, J. H. Anoxemia secondary to polycythemia and polycythemia secondary to anoxemia. *Am. J. Med.*, 19: 958, 1955.

⁵ RICHTER, T., WEST, J. R. and FISHMAN, A. P. The syndrome of alveolar hypoventilation and diminished sensitivity of the respiratory center. *New England J. Med.*, (In press.)

⁶ NEWMAN, W., FELTMAN, J. A. and DEVLIN, B. Pulmonary function studies in polycythemia vera. *Am. J. Med.*, 11: 706, 1951.

with respiratory depression and since no other mechanism is apparent, these cases do appear to be instances of primary anatomic injury to the respiratory center.

In contradistinction to the sparsity of evidence for anatomic injury to the respiratory center is the large body of observations which support the role of chronic carbon dioxide retention in accomplishing physiologic depression of the respiratory center. As examples, one may cite the decrease in sensitivity to the P_{CO_2} stimulus during sleep [7], and during prolonged residence in ambient air enriched with carbon dioxide [8]; in the latter instance, normal sensitivity is restored after the subject returns to carbon dioxide-free ambient air. Evidence also exists that diminished sensitivity of the respiratory center is a mechanism which makes possible the prolonged submersion of diving mammals [9]. This concept of a functional diminution in sensitivity to the P_{CO_2} stimulus has been carried over to patients with chronic obstructive pulmonary emphysema. However, in these subjects obstructive disease of the tracheobronchial tree and impaired ventilatory function of the chest bellows complicate assessment of the role of diminished sensitivity of the respiratory center in limiting minute ventilation.

Within the last few years, as a result of renewed interest in estimating the work of breathing, considerable insight has been gained into the role of the chest bellows in producing alveolar hypoventilation. For this type of evaluation the concept of "chest bellows" has been broadened to include not only the thoracic cage but also the adjacent structures involved in breathing, such as the diaphragm, the abdominal panniculus and the abdominal contents. Failure of the chest bellows to accomplish adequate ventilation has been described in various clinical situations: encasement of the normal lungs by an envelope

of inelastic tissue [10], obesity [11-14], and conversion of the resilient chest bellows into a rigid ankylotic structure during the course of arthritis or by disease of the vertebral column [15,16].

In Figure 3 is illustrated the work of breathing in: (1) an obese patient, (2) a patient with advanced kyphoscoliosis, and (3) a patient with severe ankylosing spondylitis. For the sake of reference, the work of breathing of a normal subject is also included. In such studies the total work of breathing is estimated by passively ventilating the relaxed patient in a body respirator while recording tidal volumes and intra-respirator pressures. Work done on the lung alone is estimated from simultaneously recorded intra-esophageal pressures; work done by the chest bellows is calculated as the difference between the total work and the work done on the lung.

The response of these three patients is similar in many respects. At lower levels of ventilation, work done on the lung remains fairly normal; however, even at these levels work done in moving the chest bellows is abnormally high. As the tidal volume is increased, the total work of breathing increases markedly, affecting predominantly, but not exclusively, the work of the chest bellows.

Before proceeding further, four simple concepts concerning the work of breathing warrant emphasis: (1) the work of breathing is done against two general types of resistance: elastic and inelastic, (2) the work against elastic resistance is increased as the square of the tidal volume, (3) the work against inelastic resistances is increased in direct proportion to an increase in respiratory frequency, and (4) the breathing pattern adopted by any particular subject is automatically adjusted to minimize the work of

⁷ MILLS, J. N. Changes in alveolar carbon dioxide tension by night and during sleep. *J. Physiol.*, 122: 66, 1953.

⁸ SCHÄFER, K. E. Atmung und Säure-Basengleichgewicht bei langdauerndem Aufenthalt in 3% CO_2 . *Arch. ges. Physiol.*, 251: 689, 1949.

⁹ IRVING, L. Respiration in diving mammals. *Physiol. Rev.*, 19: 112, 1939.

¹⁰ FELTMAN, J. A., NEWMAN, W., SCHWARTZ, A., STONE, D. J. and LOVELOCK, F. J. Cardiac failure secondary to ineffective bellows action of the chest cage. *J. Clin. Investigation*, 31: 762, 1952.

¹¹ SIEKER, H. O., ESTES, E. H., JR., KELSER, G. A. and McINTOSH, H. D. A cardiopulmonary syndrome associated with extreme obesity. *J. Clin. Investigation*, 34: 916, 1955.

¹² AUCHINCLOSS, J. H., JR., COOK, E. and RENZETTI, A. D. Clinical and physiological aspects of a case of obesity, polycythemia and alveolar hypoventilation. *J. Clin. Investigation*, 34: 1537, 1955.

¹³ BURWELL, C. S., ROHL, E. D., WHALEY, R. D. and BICHELMAN, A. G. Extreme obesity associated with alveolar hypoventilation—a Pickwickian syndrome. *Am. J. Med.*, 21: 811, 1956.

¹⁴ CARROLL, D. A peculiar type of cardiopulmonary failure associated with obesity. *Am. J. Med.*, 21: 819, 1956.

¹⁵ CHAPMAN, E. M., DILL, D. B. and GRAYBILL, A. The decrease in functional capacity of the lungs and heart resulting from deformities of the chest. *Medicine*, 18: 167, 1939.

¹⁶ FISHMAN, A. P., BERGOFSKY, E. H., TURINO, G. M., JAMESON, A. G. and RICHARDS, D. W. Circulation and respiration in kyphoscoliosis. *Circulation*, 14: 935, 1956.

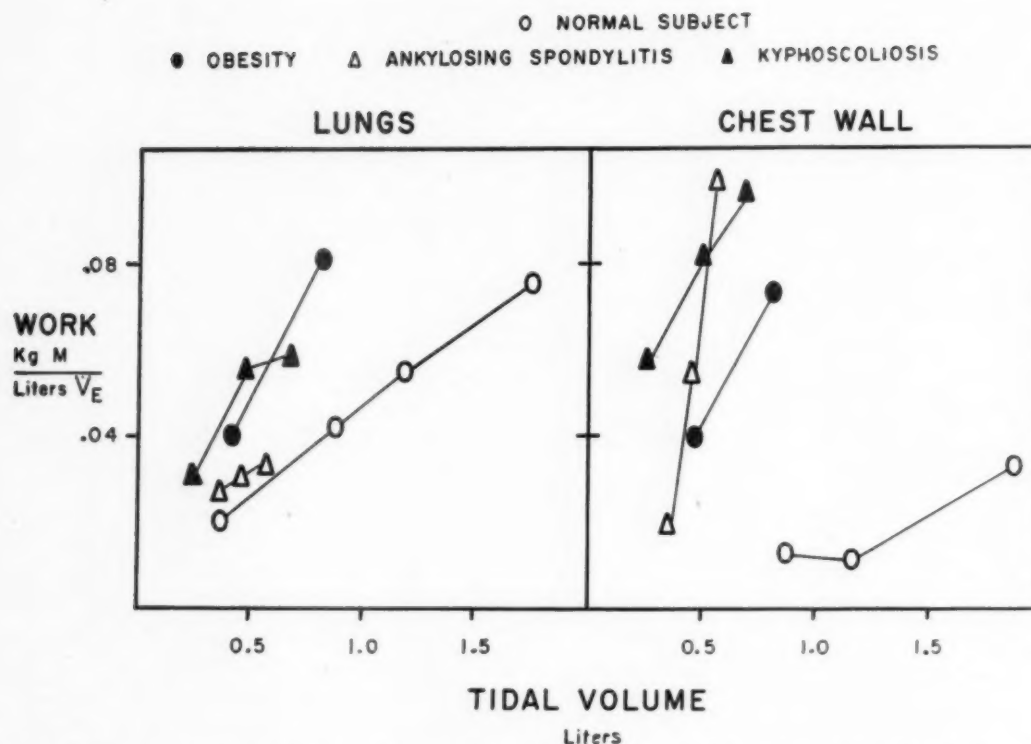


FIG. 3. The work of breathing in diseases associated with impaired function of the chest bellows.

breathing [17]. When these considerations are coupled with the experimental observations, alveolar hypoventilation emerges as an unfortunate by-product of an unconscious attempt to minimize the energy expended in breathing. The manner in which this economy is effected depends on the nature of abnormality which underlies the poor performance of the chest bellows.

Thus, patients with kyphoscoliosis have an increased elastic resistance of the lung and chest wall; they adopt a breathing pattern characterized by small tidal volumes and high respiratory rates. Such a pattern is most effective in minimizing the elastic component of the work of breathing. However, even though total ventilation is thus maintained, alveolar ventilation is sacrificed for the sake of dead space ventilation.

The obese person, on the other hand, suffers from an increase not only in elastic resistance of the lung and chest wall but also in the non-elastic resistances of the chest wall. The latter predominate, and are probably related in large part to the augmented tissue viscosity and inertial forces which are involved in mobilization of the obese abdomen, the diaphragm and the chest. Some obese individuals adopt a breathing

pattern in which total ventilation, respiratory frequency, tidal volume and alveolar ventilation are all abnormally low. Unfortunately, the natural history of obesity to the point of alveolar hypoventilation has not yet been documented. Consequently, there remains to be defined: (1) the type of obese patient in whom alveolar hypoventilation develops, (2) the transition in breathing pattern which characterizes the onset of alveolar hypoventilation, and (3) the contribution of a depressed respiratory center to the breathing pattern once carbon dioxide retention is established.

It is apparent that some subjective relief of respiratory distress (dyspnea) may be afforded the patient with impaired chest bellows by either altering the pattern of breathing or by maintaining total minute ventilation at low and more comfortable levels. It is also clear that augmented carbon dioxide levels in blood make possible a normal output of metabolic carbon dioxide despite a lowered alveolar ventilation [18] since the rate of carbon dioxide output = rate of alveolar ventilation \times per cent of carbon dioxide in alveolar air. Nonetheless, all this gain comes to naught when alveolar hypoven-

¹⁷ OTIS, A. B., FENN, W. O. and RAHN, H. Mechanics of breathing in man. *J. Clin. Investigation*, 2: 592, 1950.

¹⁸ RILEY, R. L. Editorial: the work of breathing and its relation to respiratory acidosis. *Ann. Int. Med.*, 41: 172, 1954.

tilation causes sufficient systemic hypoxemia to impose a circulatory burden.

The treatment of alveolar hypoventilation in patients with normal lungs is based on the foregoing considerations. Except for relief of immediate problems, such as congestive heart failure and/or respiratory infection, the aim of treatment is an increment in alveolar ventilation; the particular method used to accomplish this goal depends on the initiating mechanism.

A variety of mechanical aids are available to assist the patient in achieving an increase in minute and alveolar ventilation. Thus, in instances of complete paralysis of the respiratory muscles, substitution of an automatic respirator for the patient's chest bellows may be necessary. In other instances, as in the obese individual, voluntary hyperventilation or an apparatus triggered by the patient's own inspiratory effort may be all that is required. The equipment to be used must be selected with care; in applying non-automatic cycling apparatus to patients with carbon dioxide retention, the inspired oxygen mixture is of paramount importance, since the breathing of pure oxygen may completely relieve the hypoxic stimulus and fail to provide sufficient drive for the initiation of inspiration. Finally, it may be noted that artificial respirators are generally effective in relieving alveolar hypoventilation even in patients with a severe skeletal deformity and an apparently immobile chest.

It is apparent that these mechanical measures are purely palliative. The ideal of therapy is the re-setting of the regulatory apparatus so as to effect automatically a normal alveolar ventilation. This type of response has been observed in a few subjects following relief of the inciting mechanism, e.g. obesity [11,13]. On the other hand, such a goal may be unattainable, either in

a potentially reversible situation in which the initiating mechanism or hypercapnia is allowed to persist or, if irreversible, anatomic injury has affected either the respiratory center or muscles.

A critical question with regard to prognosis and therapy is the effect of sustained hypercapnia and hypoxemia, either singly or in combination, in producing irreversible damage to the respiratory center. The few observations on obese individuals suggest that sensitivity to the P_{CO_2} stimulus may be restored following weight loss and relief of carbon dioxide retention. However, the degree of reversibility which may be anticipated in other types of alveolar hypoventilation remains to be established.

Finally, experience with intrinsic disease of the lung suggests that drugs may offer the prospect of either increasing the sensitivity of the respiratory center to chemical stimuli or directly stimulating it to the generation of a greater ventilatory drive. However, at the present time it may be categorically stated that the best means for reversing a depression of the respiratory center elicited by hypercapnia is the prompt relief of the hypercapnia by mechanical hyperventilation.

Alveolar hypoventilation due to inadequate performance of the chest bellows has been, and promises to remain, a fruitful concept. Under its cloak have now been gathered many diverse clinical disorders characterized by impaired regulation of ventilation; others undoubtedly exist and await recognition.

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Presbyterian Hospital, New York, New York*

Clinical Studies

Potassium Movement in Normal Subjects*

Effect on Muscle Function

DAVID GROB, M.D., ÅKE LILJESTRAND, M.D.† and RICHARD J. JOHNS, M.D.

Baltimore, Maryland

POTASSIUM ions have an important role in muscle function. The excitability and contractility of muscle are strongly influenced by the concentration of potassium within and outside of the muscle cell, and both excitation and contraction result in the movement of this ion across the muscle membrane.

In experimental animals the resting muscle fiber normally has a potential difference of approximately 90 millivolts (mV.) between the two sides of the surface membrane, the inner surface being negative with respect to the outer surface [1,2]. It is therefore said to be in a state of polarization. Stimulation of the muscle fiber through its motor nerve results in the release from the motor nerve endings of acetylcholine (ACh), which depolarizes the fiber in the region of the motor end-plate. This initiates a wave of depolarization and subsequent repolarization, termed the muscle action potential, which is propagated along the muscle fiber and, in turn, initiates muscle contraction. Depolarization appears to be due to a temporary increase in permeability of the muscle membrane to sodium ions, allowing them to penetrate into the cell. Repolarization is accomplished by an outward flow of potassium ions [3]. The resting muscle membrane potential is believed to be proportional to the logarithm of the ratio between the intracellular and extracellular concentrations of potassium. Increasing this ratio by lowering the concentration of potassium in Ringer's solution bathing isolated muscle increases the membrane potential, while decreasing the ratio by raising the extracellular concentration or lowering the

intracellular concentration has the opposite effect [1,2].

Muscle membrane potentials have not yet been measured in man. Therefore, direct information is not available concerning their role in abnormalities of skeletal and cardiac muscle function associated with disturbances in potassium metabolism, such as hyperkalemia due to renal insufficiency; hypokalemia due to administration of insulin and glucose or of adrenal cortical hormones; excessive loss of potassium in urine, stools or vomitus; deficient intake; or familial periodic paralysis. The role of the ratio of intracellular to extracellular concentration of potassium has been difficult to assess because of the paucity of precise information concerning the concentration of this ion in the muscle cells. Indirect evidence has indicated that there is an increase in intramuscular concentration following the administration of potassium chloride [4,5] or epinephrine [6] to experimental animals, and a decrease following potassium depletion [7], exercise [8], or the administration of glucose [8], insulin [8] or adrenal cortical hormones [9] to animals or man.

In this communication a report is made of the effect of muscle contraction, rest, and the administration of glucose, insulin, epinephrine and potassium chloride on movement of potassium and skeletal muscle function in man. Movement of potassium was detected by measuring changes in the difference between the arterial and venous plasma concentrations of this ion in the forearm. Since muscle constitutes the greatest part of metabolically active

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tissue in the forearm, this movement was ascribed to changes in the concentration of potassium in the muscle cells. The influence of alterations in the intracellular and extracellular concentrations of potassium on muscle function was determined by measurement of muscle responsiveness and contractility, and of ease of depolarization by the intra-arterial injection of ACh or neostigmine, which produce prompt depression of muscle function due to persistent depolarization in the region of the motor endplates [10-12]. An increase in this depolarizing action was considered to be compatible with diminished membrane potential (depolarization), and a decrease with heightened membrane potential (hyperpolarization). Such a correlation has been demonstrated in the experimental animal following partial depolarization of the muscle membrane by a cathodal current, and following hyperpolarization by an anodal current [13].

Evidence of movement of potassium out of muscle occurred following muscle contraction or the administration of insulin. Evidence of movement into muscle occurred following the administration of glucose or potassium chloride, and possibly following rest or the administration of epinephrine. Tetanic muscle contraction or administration of potassium chloride, which were believed to decrease the ratio of intracellular to extracellular concentration of potassium, resulted in heightened muscle contractility and greater ease of depolarization by ACh, compatible with decreased membrane potential. Administration of insulin, which was believed to increase the concentration ratio, resulted in slight resistance to depolarization by ACh, compatible with increased membrane potential.

METHODS

Blood was drawn without stasis from the brachial artery and deep antecubital vein of fasting normal subjects through inlying 20-gauge Cournand-Riley needles into syringes containing 1 per cent sodium heparin in the dead space. The blood was promptly centrifuged for twenty minutes at 2,000 r.p.m., and the plasma recentrifuged twice. Plasma potassium concentration was determined in duplicate or triplicate by a flame photometer [14] in samples which showed no visible hemolysis, with four separate photometer readings of each diluted sample. The standard deviation of parallel replicate determinations was 1 per cent, and of replicate determinations on separate days, 3 per cent. Correction was made for dilution with an anticoagulant.

An average of two paired samples of arterial and venous blood was obtained before each procedure, and an average of four paired samples obtained after each procedure designed to study the movement of potassium. Paired samples were usually drawn less than one minute apart. A positive arteriovenous difference indicated uptake of potassium in the forearm drained by the venous blood, a negative difference indicated loss of potassium from the forearm, and lack of difference indicated the absence of detectable net uptake or loss. Since blood flow was not measured, the rate of uptake of potassium (blood flow times positive arteriovenous difference) or the rate of loss (blood flow times negative arteriovenous difference) could not be calculated. However, the direction of movement of the ion at any time was indicated by the arteriovenous difference, and change in the direction of movement, which was analyzed on the basis of paired experiments, could be determined. Change from a negative arteriovenous difference, or from zero, to a positive difference indicated uptake of potassium by the forearm, and change from a positive arteriovenous difference, or from zero, to a negative difference indicated loss of the ion from the forearm. Widening of a negative arteriovenous difference indicated further loss of the ion from the forearm, and widening of a positive difference indicated further gain, only if the blood flow could be assumed not to have decreased.

Drugs were injected into the brachial artery through the indwelling needle, as previously described [10]. These included insulin (Squibb), epinephrine hydrochloride (Winthrop), hydrocortisone hemisuccinate (Upjohn), acetylcholine chloride (Merck) and neostigmine methylsulfate (prostigmin,[®] Hoffmann-La Roche). The volume of injection was 2 ml. in all instances, dilutions being made with isotonic saline solution. Immediately preceding each injection the pressure in a blood pressure cuff placed about the upper arm was raised to 300 mm. Hg to occlude the artery. The injection was made as rapidly as possible, and the pressure in the cuff immediately released. The pressure was then raised to just above venous pressure for two to three minutes in order to retard escape of the drug into the systemic circulation. The intra-arterial injection of isotonic saline solution and constriction of the upper arm in the manner described did not significantly alter the potassium concentration in venous or arterial plasma obtained following release of the cuff.

Muscle function was studied by percutaneous electrical stimulation of the ulnar nerve with supra-maximal pulses and by recording the evoked muscle action potentials and isometric tension from the adductor pollicis brevis. Muscle action potentials and muscle tension produced in this way will be referred to as evoked or induced potentials and tension. The details of nerve stimulation and of muscle action potential recording have been described [10]. Isometric tension was recorded with the aid of a transducer tube myograph attached to the thumb by a chain and stirrup

[15]. To determine the effect of drugs such as ACh or neostigmine on the muscle response to nerve stimulation, these were injected into the brachial artery during intermittent stimulation of the ulnar nerve. Except when otherwise indicated, the standard pattern consisted of trains of four stimuli (interval between each stimulus, forty milliseconds) delivered every two to ten seconds. The injection was usually given after the fourth such train, so that a suitable period of response to nerve stimulation was recorded as a control.

RESULTS

PLASMA CONCENTRATION

This was determined in twenty-three subjects on thirty-eight days. Prior to the insertion of cannulas into the brachial artery and deep antecubital vein the subjects had been engaged in normal activity. Blood samples were obtained five minutes after cannulation. The mean concentration of potassium in the arterial plasma was 4.43 ± 0.06 (standard error of mean) mEq./L., and in the venous plasma 4.54 ± 0.08 mEq./L. The venous concentration was higher than the arterial concentration in twenty-three determinations, lower in seven, and not significantly different in eight. The mean arteriovenous difference was -0.11 ± 0.04 mEq./L., which indicated a slight, but significant ($P < 0.01$) loss of potassium from the forearm.

FACTORS WHICH MAY CAUSE MOVEMENT OF POTASSIUM OUT OF MUSCLE

Muscle Contraction. Intermittent muscle contraction evoked by supramaximal stimulation of the ulnar nerve by a train of four stimuli (forty milliseconds apart) repeated every two and one-half seconds for one and a half minutes resulted in an increase in venous potassium concentration in the exercised arm in twenty of twenty-three subjects. The mean change was $+0.25$ mEq./L., which was significant. (Table 1.) The change was maximal immediately after cessation of muscle activity, and diminished during the following three to eight minutes. There was no significant change in venous potassium concentration in the opposite arm or in arterial potassium concentration. The mean arteriovenous difference changed from 0.08 ± 0.15 to -0.27 ± 0.10 mEq./L., which was significant. In most of the range represented by the mean $\pm 2 \times$ standard error of mean, the arteriovenous difference changed from a positive value, or from zero, to a negative value, indicating loss

of potassium from the forearm. In the remainder, arteriovenous difference merely became more negative, indicating either increased loss of the ion from the forearm or a decrease in blood flow. Since muscle contraction is known to be followed by a marked increase in local blood flow [16], the former seems more likely.

The average force of each muscle contraction was 4.2 kg. Weaker contractions evoked by submaximal nerve stimulation for the same period of time resulted in less increase in venous potassium, the degree of increase being roughly proportional to the strength of muscle contraction. However, stronger contractions of 10 kg. force evoked by tetanic nerve stimulation at 25 or 50 per second for one and a half minutes resulted in approximately the same increase in venous potassium concentration as occurred following intermittent stimulation, although the increase lasted twice as long. Five to twenty minutes after either intermittent or tetanic muscle contraction the venous potassium concentration sometimes decreased for several minutes below the arterial concentration, indicating uptake of potassium by the forearm following the period of loss. Repeated muscle activity resulted in diminishing changes.

ACh. In five of seven subjects the intra-arterial injection of 5 mg. ACh produced a slight increase in venous potassium concentration in the injected extremity, but the mean change ($+0.06$ mEq./L.) was not significant. When ACh was injected during intermittent muscle contraction the mean increase in venous potassium in twenty-four subjects was 0.16 ± 0.05 mEq./L., which was not significantly different from that produced by contraction alone. ACh also produced marked local vasodilatation and visible arterialization of venous blood, as well as transient motor activity which was followed by weakness lasting from ten to twenty seconds [17].

Administration of Glucose Plus Insulin. In each of three subjects the intra-arterial administration of 20 units of insulin two hours after the ingestion of 125 gm. of glucose resulted in reduction in arterial potassium concentration by a mean of 0.87 mEq./L., and in venous potassium by a mean of 0.58 mEq./L. (Table 1 and Fig. 1.) This effect was maximal within an hour after injection. (Fig. 2.) The degree of change varied in the three subjects, so that, while the mean changes were large, they did not meet the requirement for statistical significance ($P < 0.05$). The arteriovenous potassium difference changed from a

TABLE I
EFFECT ON PLASMA POTASSIUM CONCENTRATION OF MUSCLE CONTRACTIONS, REST, AND ADMINISTRATION
OF GLUCOSE, POTASSIUM CHLORIDE, INSULIN AND EPINEPHRINE

No. of Subjects	Data	Plasma K ⁺ (mEq./L.)				
		Arterial	Venous		A-V Difference	
23	Before muscle contractions	4.42 ± 0.14	4.34 ± 0.08		0.08 ± 0.15	
	After	4.32 ± 0.11	4.59 ± 0.07		-0.27 ± 0.10	
	Change	-0.10 ± 0.06	0.25 ± 0.04		-0.35 ± 0.11	
	P	>0.1	<0.001		<0.01	
20	Before rest	4.33 ± 0.10	4.43 ± 0.09		-0.10 ± 0.05	
	After one hour rest	4.29 ± 0.09	4.30 ± 0.10		-0.01 ± 0.04	
	Change	-0.04 ± 0.05	-0.13 ± 0.05		0.09 ± 0.07	
	P	>0.4	<0.05		>0.2	
7	Before glucose (125 gm. orally)	4.34 ± 0.22	4.37 ± 0.19		-0.03 ± 0.05	
	After	4.08 ± 0.24	3.93 ± 0.25		0.15 ± 0.05	
	Change	-0.26 ± 0.06	-0.44 ± 0.09		0.18 ± 0.06	
	P	<0.01	<0.01		<0.05	
5	Before KCl (0.15 gm./kg. orally)	4.29 ± 0.15	4.29 ± 0.14		0 ± 0.05	
	Two hours after	7.15 ± 0.62	6.31 ± 0.45		0.84 ± 0.30	
	Change	2.86 ± 0.22	2.02 ± 0.34		0.84 ± 0.27	
	P	<0.001	<0.01		<0.05	
3	Before glucose and insulin (20 units intra-arterially)		Injected Arm	Opposite Arm	Injected Arm	Opposite Arm
	After	4.39 ± 0.47	4.34 ± 0.40	4.39 ± 0.36	0.05 ± 0.06	0 ± 0.11
	Change	3.52 ± 0.27	3.76 ± 0.28	3.73 ± 0.26	-0.24 ± 0.04	-0.21 ± 0.03
	P	-0.87 ± 0.33	-0.58 ± 0.32	-0.66 ± 0.29	-0.29 ± 0.05	-0.21 ± 0.09
		>0.05	>0.2	>0.1	<0.05	>0.1
3	Before epinephrine (0.1 mg. intra-arterially)	4.86 ± 0.22	5.14 ± 0.31	4.94 ± 0.16	-0.28 ± 0.25	-0.08 ± 0.08
	After	4.36 ± 0.58	4.12 ± 0.40	4.35 ± 0.38	0.24 ± 0.10	0.01 ± 0.03
	Change	-0.50 ± 0.38	-1.02 ± 0.09	-0.59 ± 0.44	0.52 ± 0.23	-0.10 ± 0.04
	P	>0.3	<0.01	>0.2	>0.1	>0.1

NOTE: Mean values ± S.E. of mean.

mean of 0.05 ± 0.06 to -0.24 ± 0.04 mEq./L., which was significant. Change in the arteriovenous difference from a positive value, or from zero, to a negative value, indicated loss of potassium from the forearm. When the arteriovenous difference merely became more negative, the change could be ascribed either to increased loss of the ion from the forearm or a decrease in blood flow. The former seems more likely. There was no significant difference between the effects of insulin in the doses administered in the injected and opposite extremities. The site of up-

take of potassium was not determined; presumably it was the liver. When the dose of insulin was increased to 40 units and the glucose increased by 30 gm. administered intravenously, there was further slight reduction in plasma potassium concentration, without any further change in the arteriovenous difference.

Following administration of insulin, intermittent muscle contraction evoked by nerve stimulation produced no change in venous potassium concentration in the exercised limb, in contrast to the increase which occurred prior to insulin.

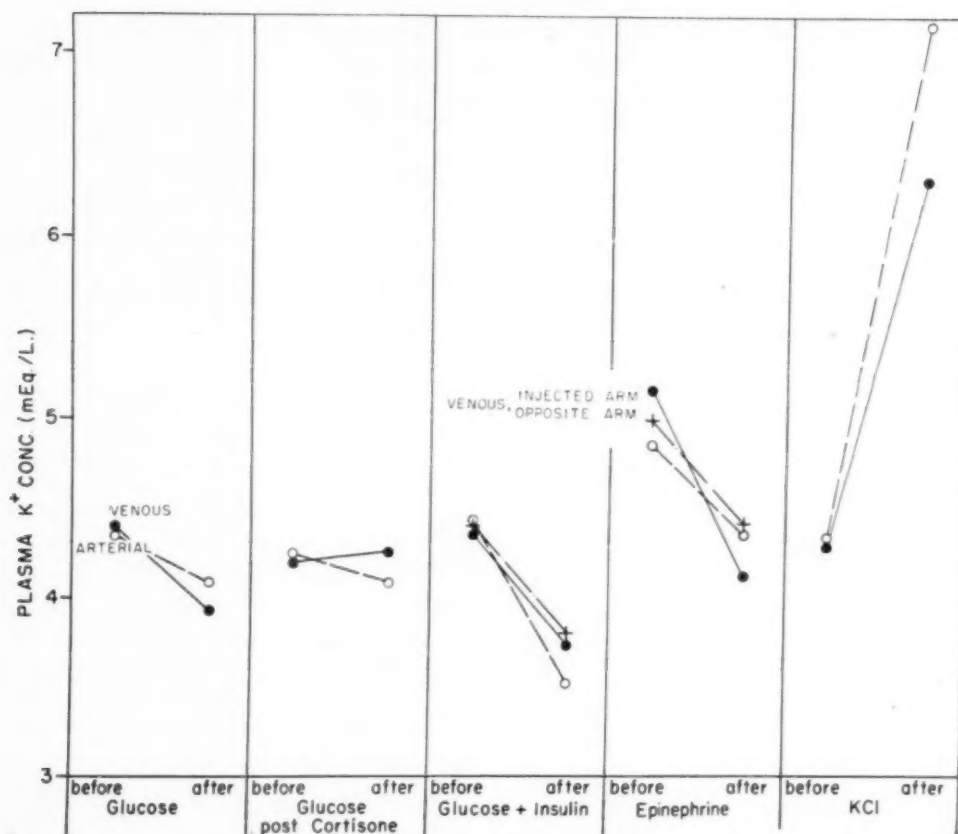


FIG. 1. Effect on plasma potassium concentration of orally administered glucose (125 gm.), glucose after cortisone, and potassium chloride (0.15 gm./kg.), and of intra-arterially administered insulin (20 units after glucose) and epinephrine (0.1 mg.). Average values are recorded.

FACTORS WHICH MAY CAUSE MOVEMENT OF POTASSIUM INTO MUSCLE

Rest. After one hour in bed, with the cannulated arm held at complete rest by means of rubber clamps, there was a reduction in venous potassium concentration in each of twenty subjects. The mean change of -0.13 mEq./L. was barely significant. (Table 1.) Arterial potassium concentration and arteriovenous difference were not significantly altered. Since the initial arteriovenous difference was negative, the reduction in venous potassium may have been due either to slight uptake of the ion by the forearm or to an increase in blood flow. The latter has not been reported to occur following rest [17]. Uptake of potassium seems more likely but cannot be proved in view of the lack of significant change in arteriovenous difference.

Administration of Glucose. Oral administration of 125 gm. of glucose resulted in reduction in arterial potassium concentration in each of seven subjects, by a mean of 0.26 mEq./L., and in venous potassium by a mean of 0.44 mEq./L.

(Table 1 and Fig. 1.) This began half an hour after ingestion of glucose, was maximal in one and a half hours, and disappeared in four hours. (Fig. 3.) The mean arteriovenous difference of potassium changed from -0.03 ± 0.05 to 0.15 ± 0.05 mEq./L. These alterations were significant. In most instances the arteriovenous difference changed from a negative value, or from zero, to a positive value, indicating uptake of potassium by the forearm. In a few instances, the arteriovenous difference merely became more positive, indicating either increased uptake of the ion by the forearm or a decrease in blood flow. The former seems more likely, as there is no reason to believe that ingestion of glucose decreases blood flow. The effect of muscle activity on venous potassium concentration was not altered.

Administration of Epinephrine. In each of three subjects the intra-arterial administration of 0.1 mg. epinephrine resulted in a fall in arterial potassium concentration by a mean of 0.5 mEq./L., and in venous potassium by a mean of 1.02 mEq./L. in the injected extremity and

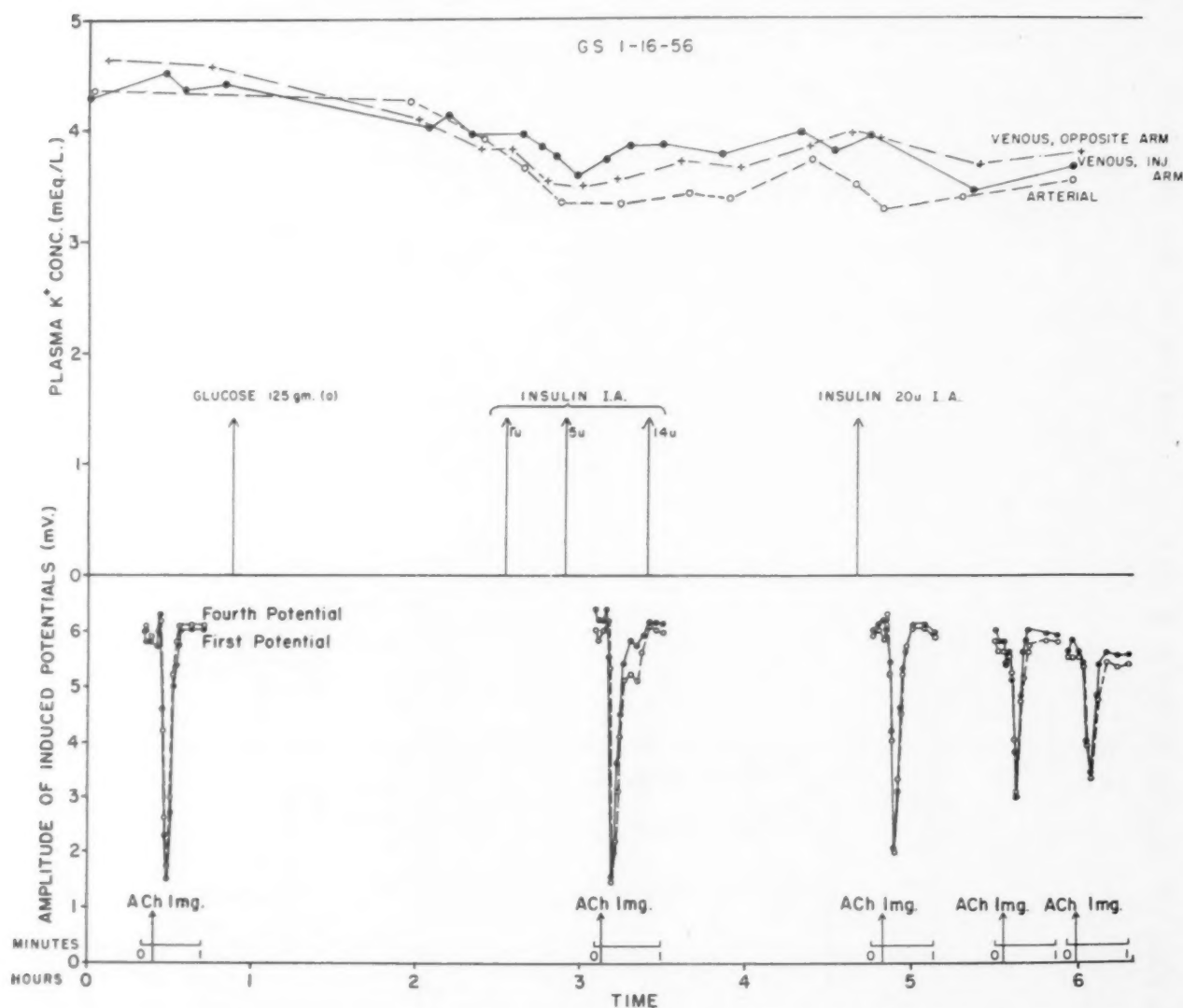


FIG. 2. Decrease in plasma potassium concentration (arterial more than venous) following administration of insulin (intra-arterially, after oral glucose), and accompanying slight reduction in the prompt depressant (depolarizing) action of intra-arterially injected ACh on muscle action potentials evoked by nerve stimulation. The amplitude of the first (●—●) and fourth (o—o) muscle action potentials in response to a train of four nerve stimuli (forty milliseconds apart) evoked every two and one-half seconds has been plotted below.

0.59 mEq./L. in the opposite arm. (Table I and Fig. 1.) This effect began ten minutes after injection, was maximal in twenty minutes, and disappeared in two hours. The mean arterio-venous potassium difference in the injected arm changed from -0.28 ± 0.25 to $+0.24 \pm 0.10$ mEq./L., and in the opposite arm from -0.08 to $+0.01$ mEq./L. The only change which was statistically significant was the reduction in venous potassium concentration in the injected arm. Since the initial arteriovenous difference was either negative or insignificant, the reduction in venous potassium may have been due either to uptake of the ion by the forearm or to an increase in blood flow. Since epinephrine

increases blood flow in muscle, while decreasing that in the skin [18], these possibilities cannot be differentiated from the available data. Similarly, it cannot be ascertained whether the more marked reduction in venous potassium in the injected extremity than in the opposite extremity was due to differences in local uptake of the ion, in blood flow, or both.

In one subject a transient increase in arterial potassium by 0.28 mEq./L. and in venous potassium by 0.13 mEq./L. occurred eight minutes after injection. The blood pressure increased by a mean of 20/6 mm. Hg for six minutes in the three subjects.

Administration of Potassium Chloride. In each

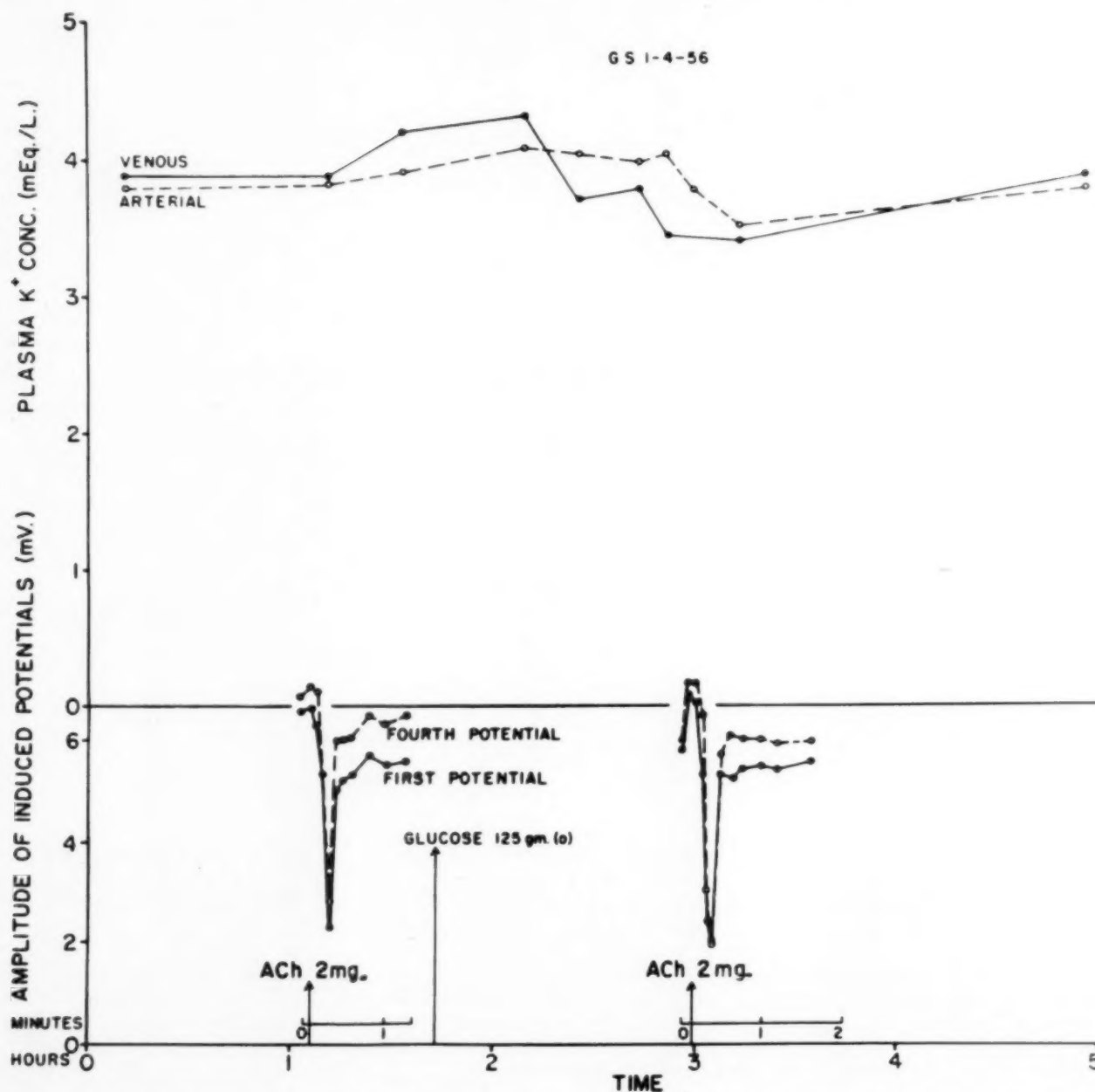


FIG. 3. Decrease in plasma potassium concentration (venous more than arterial) following oral administration of glucose, and lack of change in the prompt depressant (depolarizing) action of intra-arterially injected ACh on muscle action potentials evoked by nerve stimulation. The amplitude of the first (●—●) and fourth (○—○) muscle action potentials in response to a train of four nerve stimuli (forty milliseconds apart) evoked every two and one-half seconds has been plotted below. The increase in venous potassium concentration at the time of glucose administration is attributable to the effect of muscle contractions evoked during the initial determination of depolarizing action of ACh.

of five subjects the rise in potassium concentration following the oral administration of 9 to 12 gm. of potassium chloride (0.15 gm./kg.) was more marked in arterial plasma (mean 2.86 mEq./L.) than in venous (mean 2.02 mEq./L.) (Table 1 and Fig. 1.) The increase was maximal two hours after ingestion, and lasted five to six hours. (Fig. 4.) The arteriovenous potassium difference increased from a

mean of 0 ± 0.05 to $+0.84 \pm 0.30$ mEq./L. These alterations were significant. In most instances the arteriovenous difference changed from a negative value, or from zero, to a positive value, indicating uptake of potassium by the forearm. In the remainder the arteriovenous difference merely became more positive, indicating either increased uptake of the ion or a decrease in blood flow. The former seems more

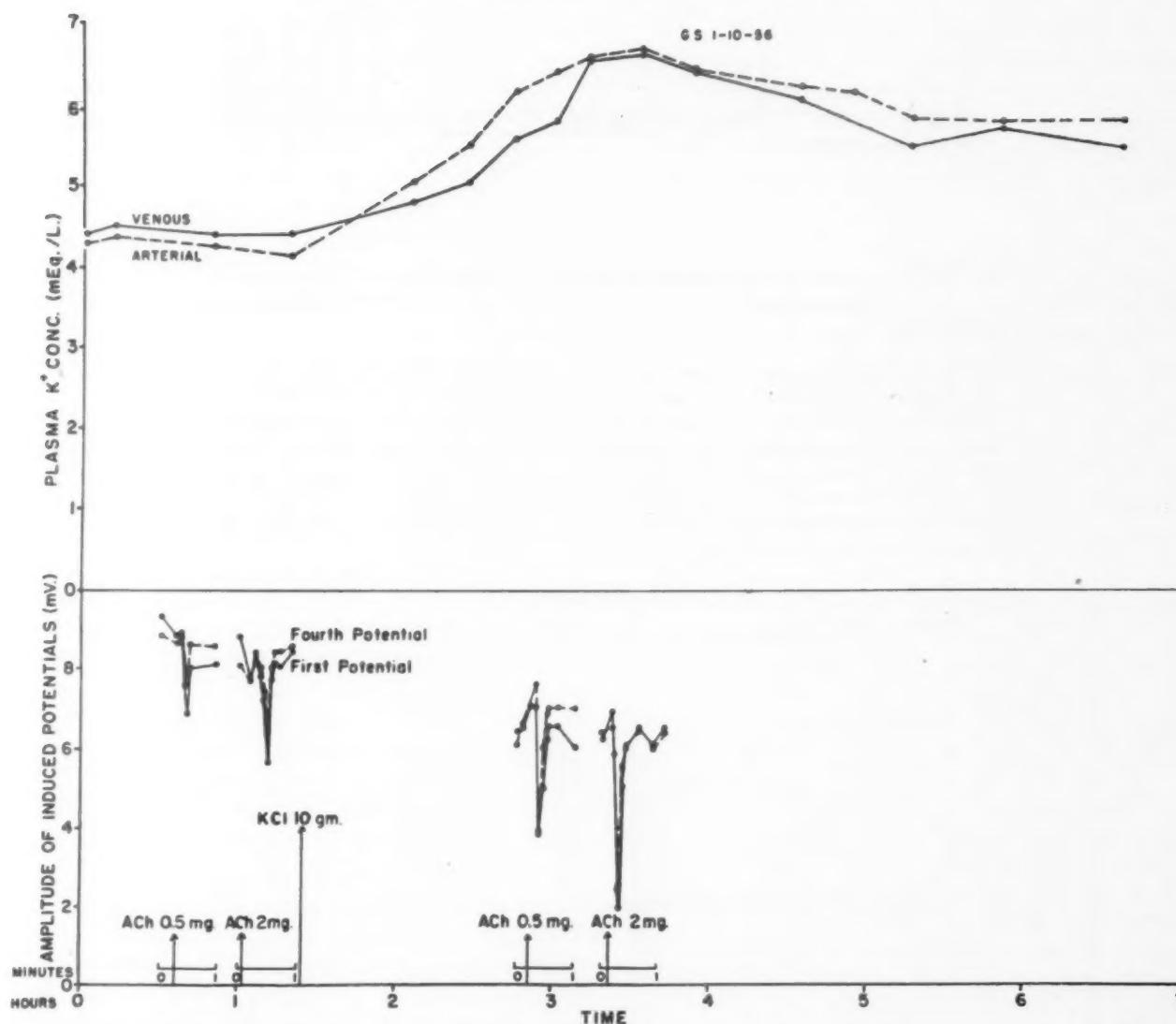


FIG. 4. Increase in plasma potassium concentration (arterial more than venous) following oral administration of potassium chloride, and accompanying increase in the prompt depressant (depolarizing) action of ACh on muscle action potentials evoked by nerve stimulation. The amplitude of the first (●—●) and fourth (○—○) muscle action potentials in response to a train of four nerve stimuli (forty milliseconds apart) evoked every two and one-half seconds has been plotted below.

likely, as there is no reason to believe that the ingestion of potassium chloride decreases blood flow.

Following administration of potassium chloride, intermittent muscle contraction evoked by nerve stimulation resulted in an increase in venous potassium concentration in the exercised limb by a mean of 0.52 ± 0.17 mEq./L., which was approximately twice as great as the increase that occurred prior to potassium administration.

EFFECT OF CORTISONE ON MOVEMENT OF POTASSIUM

The intra-arterial administration to two subjects of 50 mg. hydrocortisone hemisuccinate,

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and the oral administration to three others of 200 mg. cortisone daily for ten days, without supplemental potassium chloride, had no effect on arterial or venous potassium concentration. Cortisone had no influence on the changes in potassium concentration which occurred following the administration of potassium chloride or insulin, but it did diminish the effect of glucose. After hormone administration the ingestion of glucose was followed by reduction in arterial potassium concentration by a mean of 0.20 ± 0.15 mEq./L., and increase in venous potassium by a mean of 0.04 ± 0.16 mEq./L. (Fig. 1.) The arteriovenous potassium difference

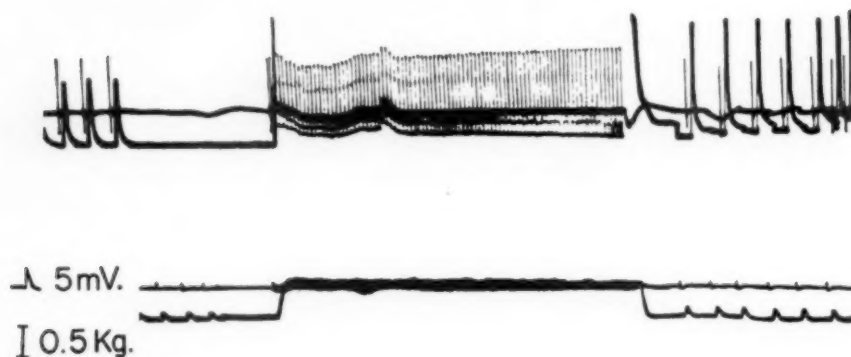


FIG. 5. Post-tetanic potentiation. (D. G., April 9, 1956.) Above: Increase in tension response of muscle (lower sweep) to a single supramaximal nerve stimulus (applied every two seconds) following tetanic contraction (9.6 kg., sweep off film) evoked by supramaximal nerve stimulation at 25 per second for ten seconds. The muscle action potential response (upper sweep) was not changed. Below: Post-tetanic potentiation much less following a weaker tetanic contraction induced by submaximal nerve stimulation. The single stimuli before and after the tetanus were also submaximal.

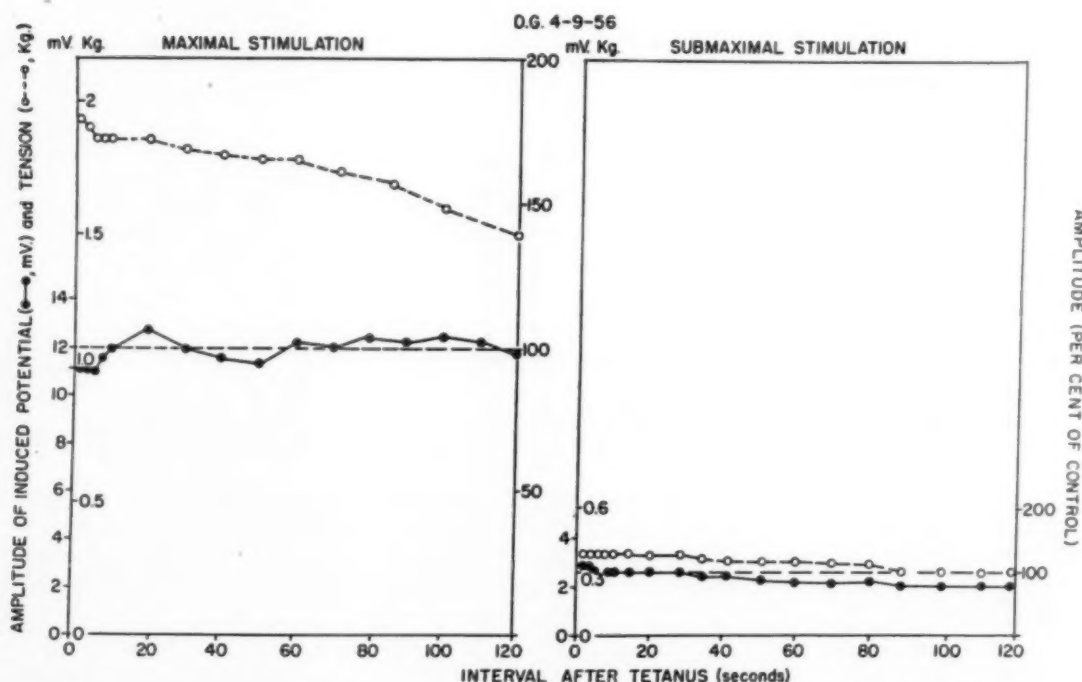


FIG. 6. Left: Time course of the increase in tension response of muscle (o—o) to a single supramaximal nerve stimulus delivered at varying intervals after tetanic muscle contraction evoked by supramaximal nerve stimulation at 25 per second for ten seconds. The muscle action potential response (●—●) was not changed. The amplitude of the tension and action potential response to a single stimulus prior to the tetanus is indicated by the broken line drawn at 100 per cent. Right: Marked decrease in post-tetanic potentiation of the tension response when the single and tetanic nerve stimuli were submaximal.

changed from a mean of $+0.05 \pm 0.04$ to -0.20 ± 0.01 mEq./L., which was significant ($P < 0.05$). This change from a positive or insignificant arteriovenous difference to a negative one indicated loss of potassium from the forearm, in contrast to the uptake which occurred prior to administration of cortisone.

MUSCLE FUNCTION

The normal muscle action potential response to single and repetitive nerve stimulation [19], and the prompt depressant effect of intra-arterially injected ACh [11] and neostigmine [12] on muscle potentials evoked by nerve stimula-

tion, have been previously described. The depressant effect of these drugs is attributable to persistent depolarization of the motor end-plate region [10-12]. Following tetanic muscle contraction or the administration of potassium chloride, which were believed to decrease the ratio of intracellular to extracellular concentration of potassium, there was an increase in the tension response of muscle to nerve stimulation and in the case of depolarization by ACh or neostigmine. Following the administration of insulin and glucose, which was believed to increase the concentration ratio, there was a slight decrease in the case of depolarization by ACh.

Effect of Single or Repeated Muscle Contractions. There was no change in the amplitude of the muscle action potential or tension response to a nerve stimulus as a result of a prior muscle contraction, or of repeated contractions evoked by intermittent nerve stimulation (train of four stimuli, each forty milliseconds apart, repeated every two and one-half seconds for one and one-half minutes).

Effect of Tetanic Muscle Contraction. There was either no change or slight increase in the muscle action potential and tension response to nerve stimulation during repetitive nerve stimulation at frequencies up to 25 per second for ten seconds, and a slight decrease during stimulation at 50 per second. Following tetanic muscle contraction evoked by repetitive nerve stimulation at a frequency of 25 or 50 per second for ten seconds, or maximal voluntary contraction for this period, there was a moderate increase in the tension response to a single nerve stimulus. (Fig. 5.) This phenomenon, termed "post-tetanic potentiation," has been attributed to the release of potassium from muscle [20]. The tension response to a single nerve stimulus was increased after tetanic contraction by a mean of 73 per cent in six subjects, and after maximal voluntary contraction by a mean of 48 per cent. (Table II.) The muscle action potential was not significantly changed. The increase in tension response began within half a second after cessation of muscle contraction, was maximal in two to four seconds, and declined over a period of three to five minutes. (Fig. 6.) It was not due to repetitive firing in response to the nerve stimulus. A decrease in the force of the tetanic contraction, evoked by submaximal nerve stimulation or by maximal stimulation at such a high frequency (for example, 200 per second)

that the contraction was not sustained, or a decrease in the force of voluntary contraction, resulted in diminution in the degree and duration of the post-tetanic potentiation. When the force of the contraction was less than one-third that produced by maximal nerve stimulation

TABLE II
MUSCLE ACTION POTENTIAL AND TENSION RESPONSE TO A SINGLE NERVE STIMULUS BEFORE AND FOUR SECONDS AFTER TETANIC CONTRACTION ELICITED BY NERVE STIMULATION AT 25 PER SECOND, OR MAXIMAL VOLUNTARY CONTRACTION LASTING TEN SECONDS

Number of Studies in Six Subjects	Data	Muscle Action Potential (mV.)	Tension (kg.)
6	Before tetanic contraction	12.8 ± 0.9	2.0 ± 0.2
	After	13.6 ± 1.3	3.4 ± 0.3
	Per cent increase	6 ± 4	73 ± 10
	P	>0.1	<0.001
16	Before maximal voluntary contraction	12.3 ± 0.8	1.35 ± 0.13
	After	12.8 ± 0.8	2.0 ± 0.21
	Per cent increase	4 ± 2	48 ± 10
	P	>0.05	<0.001

NOTE: Mean values ± S.E. of mean.

there was only slight post-tetanic potentiation of the response to a supramaximal or submaximal stimulus. (Figs. 5 and 6.) A decrease in the duration of the contraction to less than one second had a similar effect. Repeated tetanic or voluntary contractions, or prolonged contraction lasting a minute or more, were also followed by diminution in the degree of post-tetanic potentiation.

Effect of Potassium Chloride. There was an increase in the tension response to a single nerve stimulus in each of four subjects, by a mean of 0.25 kg. (20 per cent), one to two hours after the ingestion of potassium chloride. The action potential response was either unchanged or slightly reduced, and the grip strength was unchanged.

Effect of Glucose, Insulin and Epinephrine. Following the doses administered and the levels of hypokalemia attained (lowest 3 mEq./L.)

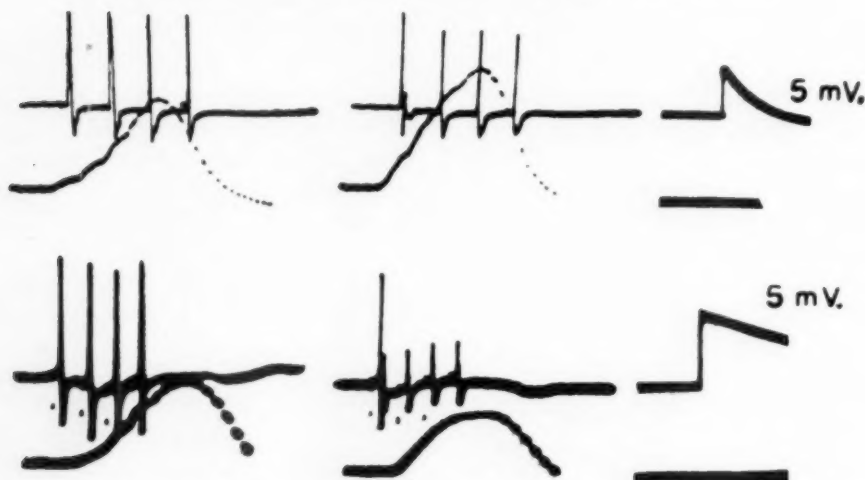


FIG. 7. Increase in the depressant action of intra-arterially injected neostigmine (0.1 mg.) following the administration of potassium chloride (0.15 gm./kg. orally). Above: Muscle action potentials (upper sweep) and tension (lower sweep) evoked by four nerve stimuli, forty milliseconds apart, before (left) and after neostigmine (right). The increase in tension response is due to repetitive firing. (E. M., June 23, 1955.) Below: Same after administration of potassium chloride. (E. M., January 26, 1956.)

there was no change in muscle response to nerve stimulation or in grip strength.

EASE OF DEPOLARIZATION BY ACh OR NEOSTIGMINE

Effect of Tetanic Muscle Contraction. Following tetanic muscle contraction evoked by repetitive nerve stimulation at 25 or 50 per second for one minute there was a moderate increase in ease of depolarization by ACh, as indicated by an increase in the prompt depressant action of this compound on evoked muscle action potentials. In two subjects 1 mg. of ACh injected intra-arterially depressed muscle action potentials evoked by nerve stimulation an average of 3.4 mV. (42 per cent) three minutes after tetanic contraction, compared to 2 mV. (23 per cent) prior to contraction.

Effect of Potassium Chloride. In three of five subjects there was an increase in ease of depolarization by ACh (Fig. 4), and, in all, by neostigmine (Fig. 7), as indicated by an increase in the prompt depressant action of these compounds on evoked muscle action potentials one to two hours after the oral administration of potassium chloride. There did not seem to be a correlation between this effect and the degree of hyperkalemia.

Effect of Glucose and Insulin. Following the administration of glucose there was no change in ease of depolarization by ACh. (Fig. 3.) However, following the administration of glucose and insulin slight resistance to depolariza-

tion developed, as indicated by a decrease in the prompt depressant action of ACh on muscle action potentials evoked by nerve stimulation. (Fig. 2.)

ELECTROCARDIOGRAPHIC CHANGES

Following the administration of potassium chloride there was an increase in amplitude and peaking of the T waves. Following the administration of glucose and insulin, and reduction of arterial potassium concentration below 3.3 mEq./L., the characteristic electrocardiographic changes of mild hypokalemia appeared. The first to be recorded was a positive after-potential on the falling limb of the T wave. There was also slight prolongation of the PR, QRS and QT intervals and lowering of the T wave, although these remained within the limits of normal. Following the administration of epinephrine a positive after-potential appeared despite reduction of arterial potassium to only 3.7 mEq./L.

COMMENTS

Movement of Potassium. Measurement of changes in the arteriovenous potassium difference provided evidence of loss of the ion from the forearm following exercise or the administration of insulin, and evidence of uptake by the forearm following the administration of glucose or potassium chloride, and possibly following rest or the administration of epinephrine.

Loss of potassium from exercised muscle in experimental animals has been reported by

numerous investigators [21–24], although results in man have been conflicting [8,21,25,26]. Repeated muscle contractions were found to produce an increase in local venous concentration of this ion which was roughly proportional to the amount of muscle activity. Even ordinary activity was associated in most subjects with a slight loss of potassium from muscle, as reflected by a negative arteriovenous difference. It is probable that the increase in blood flow which follows muscle contraction [76] limits the increase in venous concentration. While tetanic muscle contraction produced a more prolonged (but not more marked) increase in venous potassium concentration than intermittent contraction, the greater increase in blood flow which occurs following the former procedure [27] makes it likely that it produced a greater loss of potassium than intermittent contraction. This is also suggested by the occurrence of potentiation of the muscle response to nerve stimulation after tetanic, but not after intermittent, muscle contraction. Loss of potassium appeared to be due to muscle contraction, rather than to the depolarization which precedes contraction, since the injection of a relatively large amount of ACh did not produce a significant increase in venous concentration of potassium. However, the increase in local blood flow produced by ACh [28] may have concealed an increase in venous potassium [29], so that the effect of ACh may have to be re-evaluated after concomitant measurement of blood flow.

Complete rest of the limb resulted in reduction in the local venous concentration of potassium. While this could be explained by either slight uptake of potassium or an increase in blood flow, the latter has not been observed to occur [77], and seems less likely. A decrease in the venous concentration of potassium has been observed during sleep in the dog [22], and a decrease in urinary excretion of the ion during sleep has been reported in man [30].

The oral administration of glucose was followed by evidence of uptake of potassium by muscle. In a similar study evidence of loss from muscle was reported, concomitant with decreased arterial concentration attributed to the entry of potassium into the liver [8]. Numerous studies *in vitro* have demonstrated that glucose enters the cells of both muscle [37] and liver [32] with potassium ions, and that this transfer is followed by the deposition of glycogen [25,33]. It seems likely that, *in vivo*, glucose enters both muscle and liver with potassium, and it is possi-

ble that the relative uptake by these tissues may vary, perhaps depending on the state of glycogen stores and of muscle activity. Potassium appears to be employed in the phosphorylation of hexose [34,35] and in the transfer of high energy phosphate from phosphopyruvate to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP), and perhaps to creatine to form creatine phosphate [34,36]. These organic phosphate compounds may be present in the cell as the potassium salts. The release of potassium during muscular exercise may be the result of their dephosphorylation, as well as of glycolysis. An increase in the amount of diffusible potassium in muscle after prolonged activity has been described [37].

The administration of insulin following glucose resulted in further lowering of plasma potassium concentration, and evidence of loss of potassium from muscle. Since the ion must have entered some other site, presumably the liver, the loss from muscle may have been secondary to reduction in the plasma concentration, and an effort by the body to maintain this concentration. Similar changes were observed by Farber [8], who also demonstrated uptake of potassium and glucose by the liver. *In vitro*, insulin increases the uptake of potassium, with glucose, by muscle as well as by liver [21,38]. Failure to demonstrate uptake of the ion by muscle following the intra-arterial injection of insulin may have been due to predominance of the effect on the liver, to the relatively large doses of insulin administered, and perhaps to a time lag which may have concealed any local effect.

The administration of epinephrine resulted in a fall in venous potassium concentration, attributable either to uptake of potassium by muscle, to increased blood flow, or both. In one subject this was preceded by a transient rise in plasma potassium which was more marked in arterial plasma. In experimental animals, epinephrine has been found to produce a rise in plasma glucose, and to a lesser extent in potassium, attributed to liver glycolysis [6,39]. This is followed by a fall in plasma potassium [40], which has also been observed in man [41], and which appears to be due to the movement of glucose, with potassium, into muscle; that is, to the net transfer of glycogen, with potassium, from liver to muscle.

The administration of potassium chloride resulted in uptake of potassium by muscle against the concentration gradient. Muscle

	NORMAL	HYPOPOTASSEMIA	HYPERPOTASSEMIA
RESTING STATE			
(mEq./L.) $\frac{K_i}{K_e}$	$\frac{-}{+} \frac{158}{45} \frac{-}{+}$	$\frac{-}{+} \frac{2}{2} \frac{-}{+}$	$\frac{-}{+} \frac{8}{8} \frac{-}{+}$
$\frac{K_i}{K_e}$	35	>35	<35
MEMBRANE POTENTIAL	NORMAL	INCREASED (HYPERPOLARIZED)	DECREASED (PARTLY DEPOLARIZED)
AFTER NERVE STIMULATION (→ ACh RELEASE) OR ACh INJECTION			
	DEPOLARIZED	RESISTANT TO DEPOLARIZATION	ABNORMAL EASE OF DEPOLARIZATION

FIG. 8. Schematic representation of observed extracellular potassium concentration (K_e) and ease of depolarization by injected ACh before and after induction of hypopotassemia and hyperpotassemia, and of presumed intracellular potassium concentration (K_i) [53], ratio of intracellular to extracellular concentration $\frac{K_i}{K_e}$, membrane potential, and ease of depolarization by ACh released

from motor nerve endings. Left, normal plasma potassium concentration. Middle, during hypopotassemia. Right, during hyperpotassemia.

activity then resulted in a greater output of the ion, probably as a result of the increased intracellular concentration or content. Following ingestion or injection [42] of potassium chloride about two-thirds of the absorbed ion leaves the extracellular fluid; the maximal serum concentration is one-third as high as would be expected were its distribution purely extracellular. Studies in animals with radioactive potassium have shown that administered potassium is first rapidly taken up by the liver and kidneys, and then slowly released to other tissues, including the muscles, which are capable of storing large amounts of the ion, at least temporarily [4,5,43].

The intra-arterial injection of hydrocortisone or the oral administration of cortisone for several days had no effect on arterial or venous potassium concentration. More prolonged administration is known to reduce plasma [9] and muscle [44] concentration. Cortisone markedly inhibited the uptake of potassium by muscle following the ingestion of glucose but had less effect on the disappearance of potassium from arterial plasma into some other site, presumably the liver. Cortisone inhibits glycogenesis in both muscle and liver in experimental animals [9].

Role of the Ratio of Intracellular to Extracellular Concentration of Potassium in Muscle Function. The increase in tension response of muscle and in the ease of depolarization by ACh or neostigmine observed after tetanic muscle contraction or after the administration of potassium chloride is probably due, at least in part, to a decrease in the resting muscle membrane potential resulting from a decrease in the ratio of intracellular to extracellular concentration of potassium. (Fig. 8.) Tetanic muscle contraction in animals [20] and man [45], and the intra-arterial administration to animals of a suitable concentration of potassium chloride [20,46], are known to produce an increase in the tension response of muscle to a nerve stimulus, without increase in the muscle action potential response. The latter is not surprising, since a supra-maximal nerve stimulus elicits an action potential in all innervated muscle fibers, each of which responds by a potential of maximal amplitude; that is, in an all-or-none manner. On the other hand, the contractile response of the muscle fiber is not all-or-none. The increase produced by such measures as potassium administration has been termed the "treppe" or "staircase"

effect. Both tetanic contraction and administration of potassium result in a decrease in muscle membrane [20] and end-plate [47,48] potentials. These similarities support the suggestion that post-tetanic potentiation is due, at least in part, to the release of potassium ions from muscle with contraction [20]. The resulting reduction in the ratio of intracellular to extracellular concentration of potassium would account for lowering of the membrane potential. This change, as well as reduced intracellular potassium concentration, has been found to favor contraction of actomyosin [49,50]. Post-tetanic potentiation cannot be attributed to the release of ACh which occurs prior to contraction. Not only does the long duration of the potentiation make this unlikely but the injection of ACh did not produce an increase in the response of muscle to a nerve stimulus. In addition, there was a decrease in post-tetanic potentiation when the frequency of nerve stimulation was increased to the point where muscle contraction was no longer sustained. Therefore, post-tetanic potentiation is a postjunctional (muscle fiber) phenomenon, and probably due, at least in part, to the release of potassium from muscle and the resulting reduction in concentration ratio of potassium and in membrane potential along the entire muscle. ACh, in contrast, reduces the muscle membrane potential only in the region of the motor end-plate [48].

Following ingestion of potassium chloride the increase in depolarizing action of ACh was neither striking nor uniform. It is likely that the increase in the concentration ratio was not marked, not only because of the moderate levels of hyperkalemia attained but also because of the almost simultaneous increase in the intracellular and extracellular concentrations of the ion. The latter may account for the infrequency of severe weakness in hyperkalemia, and for the occurrence of less severe alterations in skeletal muscle and cardiac function when there is gradual elevation in plasma potassium concentration than when the same level is rapidly attained [42].

The slight resistance to depolarization by ACh observed during hypokalemia induced by the administration of glucose and insulin is attributable to an increase in the muscle membrane potential. (Fig. 8.) This increase may have been limited not only by the moderate levels of hypokalemia attained, but also by the almost simultaneous decrease in the concentration of

potassium on the two sides of the muscle membrane. Such limitation may account for the infrequency of severe weakness in hypokalemia due to glucose and insulin [51], adrenal cortical hormones [9], or excessive loss or deficient intake of potassium [52], and for the occurrence of less severe alterations in skeletal muscle and cardiac function when there is a gradual diminution in plasma potassium concentration than when the same level is rapidly attained [52].

Measurement of post-tetanic potentiation and of ease of depolarization by ACh and other depolarizing compounds should prove useful in the study of disorders of potassium metabolism associated with weakness.

SUMMARY

Study in normal subjects of potassium movement and associated changes in skeletal muscle function yielded the following results:

1. Muscle contraction caused movement of potassium out of muscle, as indicated by change in the arteriovenous difference in the exercised extremity. There was some evidence to suggest that rest had the opposite effect.

2. During hypokalemia following administration of glucose, and possibly following epinephrine, there was evidence of movement of potassium into muscle, while following insulin there was evidence of movement of the ion out of muscle and into some other site, presumably the liver.

3. Hyperkalemia produced by administration of potassium chloride was accompanied by movement of potassium into muscle. Muscle contraction then caused greater loss of potassium from the exercised extremity.

4. Following tetanic muscle contraction or the administration of potassium chloride, and concomitant with a probable decrease in the ratio of intracellular to extracellular concentration of potassium, there was an increase in muscle contractility and in the ease of depolarization by ACh or neostigmine. These changes are attributed to a reduction in the resting muscle membrane potential resulting from the decrease in concentration ratio.

5. Following the administration of insulin and glucose, and concomitant with a presumed increase in the concentration ratio of potassium, there was a slight decrease in the ease of depolarization by ACh. This change is attributed to an increase in the resting muscle membrane potential resulting from the increased concentration ratio.

6. It is suggested that severe weakness may be infrequent in hyperkalemia, and in hypokalemia due to deficient intake or excessive loss of potassium or the administration of insulin and glucose, because the intracellular concentration of potassium may change in the same direction as the extracellular concentration in each instance, tending to limit the change in concentration ratio.

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Potassium Movement in Patients with Familial Periodic Paralysis*

Relationship to the Defect in Muscle Function

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THE preceding communication [7] dealt with factors affecting the movement and intracellular to extracellular concentration ratio of potassium in normal subjects, and with the influence of the concentration ratio on contractility and ease of depolarization of skeletal muscle. It was observed, in normal subjects, that evidence of movement of potassium out of muscle occurred following muscle contraction or the administration of insulin, while evidence of movement into muscle occurred following the administration of glucose or potassium chloride, and possibly following rest or the administration of epinephrine. Tetanic muscle contraction or administration of potassium chloride, which was believed to decrease the ratio of intracellular to extracellular concentration of potassium, resulted in heightened muscle contractility and greater ease of depolarization by ACh. This was attributed to a decrease in the resting membrane potential. Administration of insulin, which was believed to increase the concentration ratio, resulted in slight resistance to depolarization by ACh, attributable to an increase in the membrane potential. It was suggested that the changes in concentration ratio and muscle function following the administration of potassium chloride or insulin were relatively small not only because of the moderate levels of hyperkalemia and hypokalemia attained, but also because the intracellular concentration of potassium may have changed in the same direction as the extracellular concentration in each instance.

In the present communication similar studies

were carried out on factors affecting the movement and concentration ratio of potassium in two patients with familial periodic paralysis and in one with non-familial periodic paralysis, and on the mechanism of weakness in these diseases. Attacks of weakness in familial periodic paralysis are usually associated with a shift of potassium from the extracellular to the intracellular phase, since reduction in the plasma concentration of this ion occurs without increase in urinary excretion [2,3]. Muscle has been considered to be the most likely site of intracellular movement of the ion [4,6]; liver has also been suggested as a possible site [7,8]. The precipitation of attacks by food, especially carbohydrate, and by glucose, insulin or epinephrine [8], and the concomitant reduction in plasma inorganic phosphate [9], suggest that this transfer is associated with glucose metabolism. Whether this involves the deposition of glycogen in muscle or liver, or increased combustion of glucose, as suggested by the reported increase in plasma pyruvate concentration [10], has not been made clear. Attacks of weakness are associated with reduction or even disappearance of the response to both indirect and direct mechanical and electrical stimulation of muscle [8,11,12], and diminution in the amplitude and propagation of muscle action potentials evoked by nerve stimulation [4].

In the three patients with periodic paralysis who were studied there was evidence of abnormal uptake of potassium by muscle following intake of food, glucose, insulin and possibly epinephrine. Attacks of weakness were asso-

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ciated with reduction in the plasma concentration of this ion, abnormally high arteriovenous difference, and reduction in the muscle action potential and tension response to nerve stimulation. Evidence was obtained that the reduced responsiveness and contractility of muscle may be due to hyperpolarization of the muscle membrane resulting from an increase in the intracellular to extracellular concentration ratio of potassium.

METHODS

PATIENTS STUDIED

The methods were described in the preceding communication [7].

Two of the patients studied had the characteristic family history and manifestations of familial periodic paralysis. The majority of studies were carried out in these patients. The third patient had periodic paralysis associated with muscular dystrophy of mild degree, and no family history of muscle disorder. However, the attacks of weakness and alterations in plasma potassium concentration and movement and in muscle function in this patient were similar to those observed in the other two. In all three patients tests of thyroid function were normal.

M. H. was a fourteen year old boy who began to have intermittent attacks of weakness at the age of twelve. His maternal grandmother and two of her brothers, his mother, and two maternal uncles had suffered from similar attacks since adolescence. One uncle died at age thirty-five of respiratory paralysis during an episode of weakness. Four maternal uncles and one aunt, two younger brothers and one younger sister have not been affected by the disease.

From three times a week to once a month the patient awoke unable to move his arms, legs or neck. At other times he would awaken with less marked weakness. On only one occasion was there difficulty in swallowing and breathing. Attacks of weakness always began during sleep, and were more likely to occur after a large evening meal or excessive fatigue. In the absence of treatment, severe attacks of weakness lasted from twelve to twenty-four hours. When exercise was possible, this accelerated recovery. Milder attacks lasted from three to twelve hours. Following the oral administration of potassium chloride there was gradual return of strength in two to four hours. The daily prophylactic administration of 10 to 20 gm. of potassium chloride greatly diminished the frequency and

severity of attacks of weakness. When the patient was not in an attack, physical examination was normal. During an attack, there was weakness of the muscles of the extremities, trunk and neck, varying from a mild degree to complete flaccid paralysis, with disappearance of tendon reflexes.

A. B. was a twenty-four year old man who began to have intermittent attacks of weakness at the age of twelve. His mother, two maternal uncles and three brothers had had similar attacks since adolescence. Three maternal aunts, one uncle and one younger sister have not been affected by the disease. The frequency and character of the patient's attacks, his response to potassium chloride, and the results of the physical examination were similar to those of patient M. H.

A. R. was a thirty-two year old woman who had intermittent attacks of weakness since the age of seven. There was no family history of muscle disorder. The frequency and character of the attacks, and the response to potassium chloride, were similar to those of patients M. H. and A. B. However, in contrast to the others, in this patient slowly progressing generalized weakness developed which was present between attacks. When not in an attack there was ptosis and mild weakness and wasting of the muscles of the shoulder and pelvic girdles, extremities, trunk and face. Tendon reflexes were normal. Urinary creatine excretion was increased, up to 400 mg. a day. Pathologic examination of a biopsy specimen from the deltoid muscle showed changes characteristic of muscular dystrophy.

RESULTS

PLASMA CONCENTRATION AND MOVEMENT OF POTASSIUM

When Not in Attack. The plasma concentration of potassium was determined on fifteen occasions in the three patients, when they were fasting, eight to twelve hours after their last dose of potassium chloride, and when they were at their best strength and had been engaged in normal activity. Blood samples were obtained five minutes after cannulation of the brachial artery and deep antecubital vein. The mean arterial concentration was 4.45 ± 0.08 (standard error of mean) mEq./L.; venous concentration, 4.43 ± 0.13 mEq./L.; and arteriovenous difference, 0.02 ± 0.06 mEq./L. There was, therefore, no significant net uptake or loss of potassium in the forearm, in contrast to the

TABLE I
EFFECT ON PLASMA POTASSIUM CONCENTRATION OF MUSCLE CONTRACTION, REST, AND ADMINISTRATION
OF GLUCOSE, POTASSIUM CHLORIDE, INSULIN AND EPINEPHRINE

No. of Studies In Three Patients	Data	Plasma K ⁺ (mEq./L.)			
		Arterial	Venous		A-V Difference
8	Before muscle contraction	4.28 ± 0.07	4.00 ± 0.11		0.28 ± 0.13
	After	4.28 ± 0.08	4.10 ± 0.09		0.18 ± 0.03
	Change	0 ± 0.09	0.10 ± 0.03		-0.10 ± 0.13
	P for change	<0.02		>0.5
	P for difference from normal subjects	>0.3	<0.01		>0.1
5	Before muscle contraction during attack	2.55 ± 0.26	2.35 ± 0.20		0.20 ± 0.14
	After	2.52 ± 0.27	2.75 ± 0.20		-0.23 ± 0.15
	Change	-0.03 ± 0.02	0.40 ± 0.06		-0.43 ± 0.07
	P for change	>0.2	<0.01		<0.01
	P for difference from change when not in attack	>0.7	<0.001		<0.05
5	Before rest	4.37 ± 0.10	4.40 ± 0.12		-0.03 ± 0.06
	After one hour rest	4.37 ± 0.09	4.21 ± 0.05		0.16 ± 0.08
	Change	0 ± 0.02	-0.19 ± 0.10		0.19 ± 0.08
	P for change	>0.1		>0.05
	P for difference from normal subjects	>0.4	>0.5		>0.3
4	Before glucose (125 gm. orally)	4.28 ± 0.18	4.25 ± 0.22		0.03 ± 0.13
	After	3.66 ± 0.28	3.12 ± 0.27		0.54 ± 0.14
	Change	-0.62 ± 0.28	-1.13 ± 0.25		0.51 ± 0.18
	P for change	>0.05	<0.05		<0.05
	P for difference from normal subjects	>0.2	<0.05		>0.1
8	Before KCl (0.15 gm./kg. orally) during attack	2.26 ± 0.09	2.46 ± 0.18		-0.20 ± 0.18
	Two hours after KCl	4.21 ± 0.24	4.87 ± 0.30		-0.67 ± 0.18
	Change	1.95 ± 0.24	2.43 ± 0.31		-0.48 ± 0.34
	P for change	<0.001	<0.001		>0.1
	P for difference from normal subjects	<0.02	>0.3		<0.02
1	Before insulin (20 units intra-arterially) and glucose	4.40	Injected Arm	Opposite Arm	Injected Arm
	After	3.50	4.38	4.48	0.02
	Change	-0.90	2.70	2.69	0.80
	P for difference from normal subjects	>0.9	-1.68	-1.79	0.78
			>0.05	>0.05	<0.01
1	Before epinephrine (0.1 mg. intra-arterially)	4.58	4.55	5.16	0.03
	After	3.86	3.10	3.92	0.76
	Change	-0.72	-1.45	-1.24	0.73
	P for difference from normal subjects	>0.7	<0.05	>0.2	>0.4
					<0.01

NOTE: Procedures begun when patients were not in an attack, except where indicated. Mean values ± S.E. of mean. P of difference from normal subjects is the probability associated with the difference between the recorded change and that which occurred in normal subjects [7].

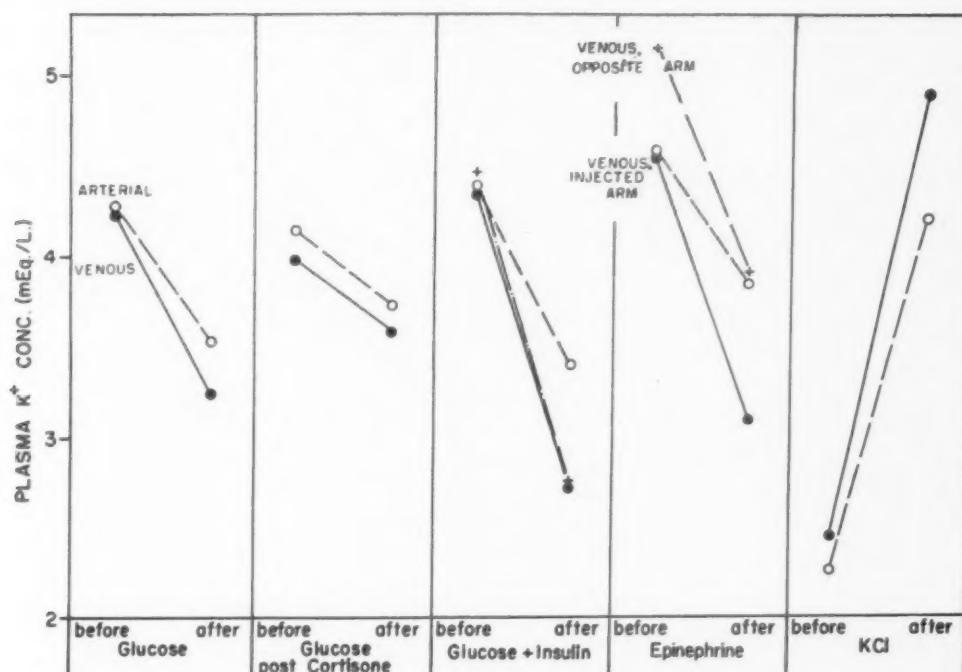


FIG. 1. Effect on plasma potassium concentration of orally administered glucose (125 gm.), glucose after cortisone, and potassium chloride (two hours after 0.15 gm./kg.), and of intra-arterially administered insulin (20 units after glucose) and epinephrine (0.1 mg.). Mean values are recorded.

slight but significant loss which was found in normal subjects [7].

Effect of muscle contraction: Intermittent muscle contractions evoked by nerve stimulation (four stimuli, each forty milliseconds apart, repeated every two and one-half seconds for one and one-half minutes) produced a mean increase in potassium concentration of 0.1 mEq./L. in venous plasma draining the exercised limb. (Table 1.) This was significantly less than the increase that occurred in normal subjects [7]. The time course was approximately the same. The mean force of each contraction (3 kg.) was three-fourths of that in normal subjects. There was no significant change in arterial potassium and arteriovenous difference in the exercised arm, or in venous potassium in the opposite arm. The increase in venous potassium in the limb exercised may have been due either to loss of potassium from the forearm or to the increase in blood flow which occurs following exercise [13].

Effect of one hour rest: After one hour in bed, with the cannulated arm held at complete rest by means of rubber clamps, the arteriovenous potassium difference changed from a mean of -0.03 ± 0.06 to 0.16 ± 0.08 mEq./L. This change was not quite significant (Table 1) nor was it significantly different from that observed in normal subjects [7].

Effect of glucose: Oral administration of 125 gm. of glucose was followed by reduction in arterial potassium concentration by a mean of 0.62 mEq./L., and in venous concentration by 1.13 mEq./L. (Table 1 and Fig. 1.) The latter change was significantly greater than in normal subjects [7]. The arteriovenous potassium difference changed from a mean of 0.03 ± 0.13 to 0.54 ± 0.14 mEq./L. Since the initial arteriovenous differences were either negative, positive or insignificant, this change could have been due either to uptake of potassium by the forearm, to a marked reduction in blood flow, or both. Since there is no reason to believe that ingestion of glucose reduces the blood flow, the former explanation seems more likely. The reduction in plasma concentration was maximal in two to four hours (Fig. 2), and lasted more than twice as long as in normal subjects.

Effect of insulin: The intra-arterial administration of 20 units of insulin two hours after the ingestion of 125 gm. of glucose resulted in reduction in arterial potassium concentration by 0.9 mEq./L., and in venous concentration by 1.68 mEq./L. in the injected forearm and 1.79 mEq./L. in the opposite one. (Table 1 and Figs. 1 and 2.) The arteriovenous differences changed from 0.02 and -0.08 mEq./L. to 0.78 and 0.89 mEq./L. This change from

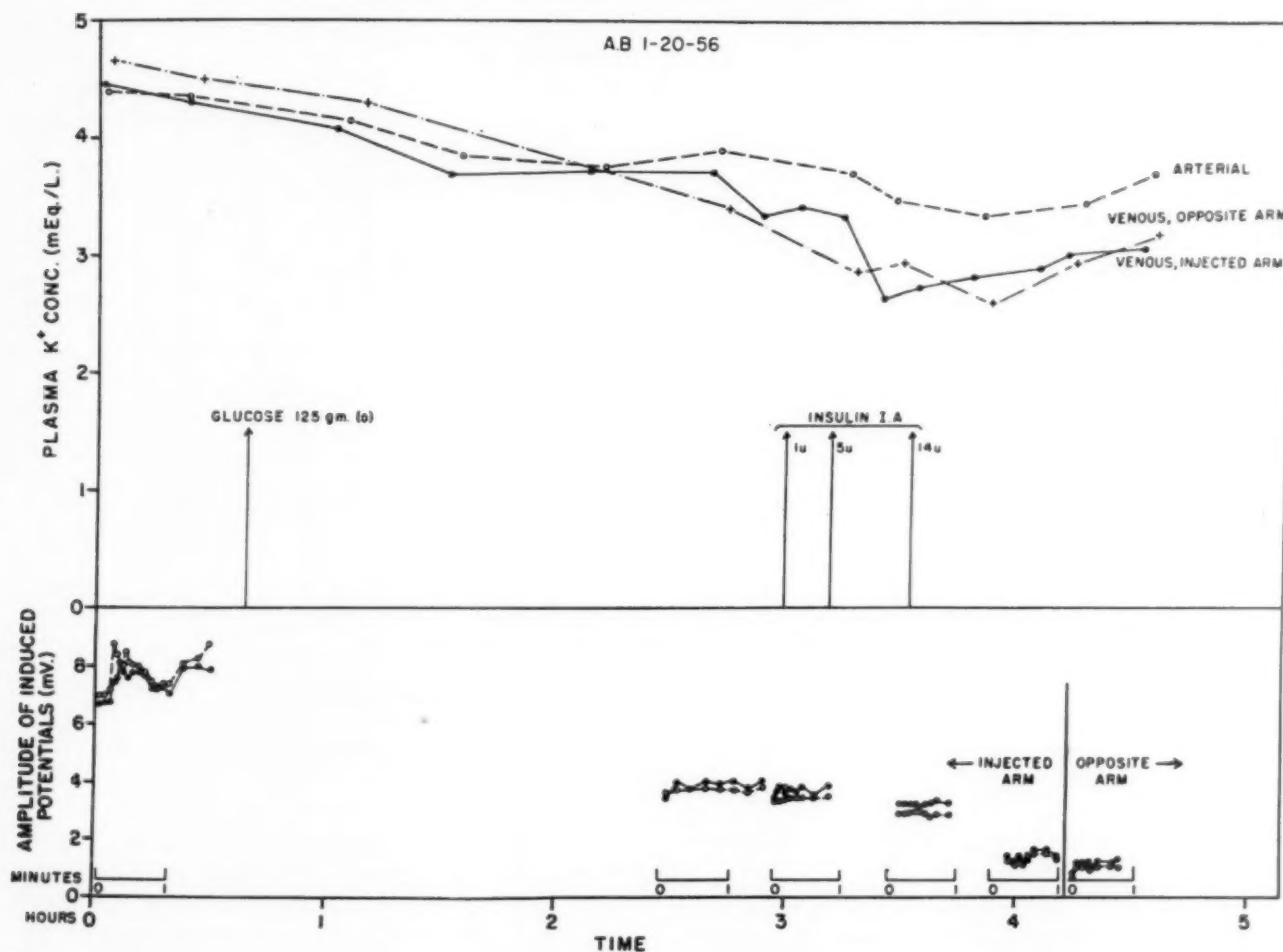


FIG. 2. Decrease in plasma potassium concentration (venous more than arterial) and in muscle action potential response to nerve stimulation following the oral administration of glucose and the intra-arterial administration of insulin. The amplitude of the first (●—●) and fourth (○—○) muscle action potentials in response to a train of four nerve stimuli (forty milliseconds apart) evoked every two and one-half seconds has been plotted below.

insignificant or negative to positive differences indicates that there was uptake of potassium by both extremities. The alterations in arteriovenous difference were significantly different from those in normal subjects, in whom there was evidence of loss of potassium from the extremity [7].

Effect of epinephrine: The intra-arterial administration of 0.1 mg. epinephrine resulted in reduction in arterial potassium concentration by 0.72 mEq./L., and in venous potassium by 1.45 mEq./L. in the injected extremity and 1.24 mEq./L. in the opposite one. (Table 1 and Fig. 1.) The arteriovenous difference in the injected arm changed from 0.03 to 0.76 mEq./L., indicating that there was uptake of potassium by this extremity. The reduction in venous potassium in the injected arm was significantly greater than in normal subjects. This is attributable either to greater uptake of potassium or

to more marked reduction in blood flow. The former seems more likely, since the reduction in venous potassium that occurred in normal subjects was attributable either to uptake of potassium or to increased blood flow [7].

The change in arteriovenous difference in the uninjected arm from -0.58 mEq./L. (an unusually high difference) to -0.06 mEq./L., which was significantly greater than in normal subjects, could have been due to local uptake of potassium, increased blood flow, or both. Since epinephrine increases blood flow in muscle of normal subjects, while decreasing that in skin [14], these possibilities cannot be differentiated from the available data.

Effect of cortisone: The intra-arterial injection of 20 mg. hydrocortisone hemisuccinate or the oral administration of 200 mg. cortisone daily for ten days, without supplemental potassium

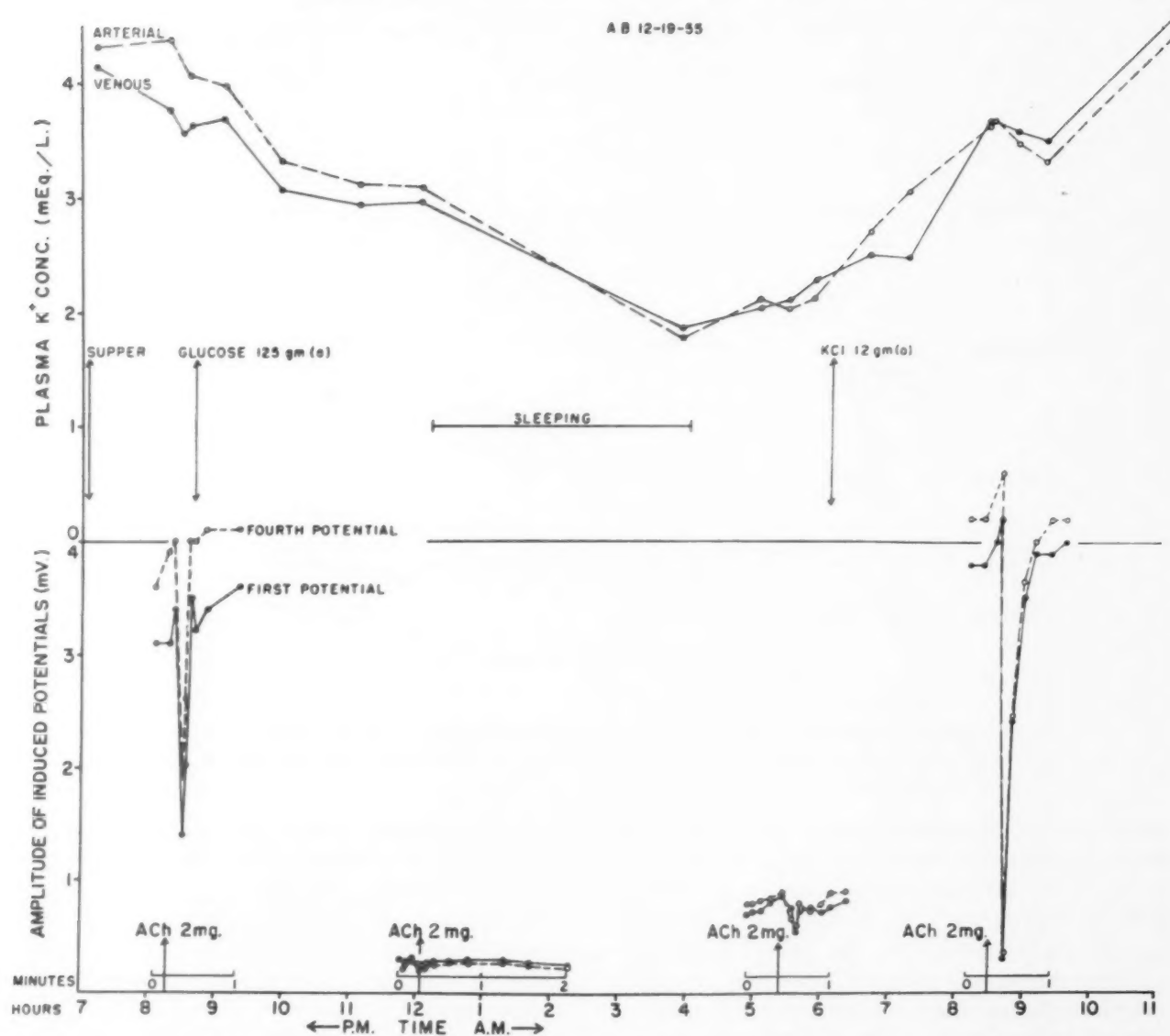


FIG. 3. Decrease in plasma potassium concentration (venous more than arterial) following supper and oral administration of glucose, marked reduction in the muscle action potential response to nerve stimulation and in the prompt depressant action of intra-arterially injected ACh on this response, and recovery following oral administration of potassium chloride. The amplitude of the first and fourth muscle action potentials in response to a train of four nerve stimuli (forty milliseconds apart) evoked every two and one-half seconds has been plotted below.

chloride, had no effect on the arterial or venous concentration of potassium. Cortisone had no appreciable influence on the effect of intra-arterial epinephrine or insulin on arterial and venous potassium concentration and on muscle strength, but it did diminish the effect of glucose and of a high carbohydrate meal. Following administration of cortisone the ingestion of glucose or food lowered plasma potassium less than one-half as much as it did prior to the administration of the hormone, and caused virtually no change in the arteriovenous difference, in contrast to the increase which occurred prior to cortisone. (Fig. 1.) Thus, as in normal

subjects [7], the hormone inhibited uptake of potassium by the forearm.

Changes during "Spontaneous" or Induced Attacks of Paralysis. These occurred during the night, or were induced during the day or night, after the patients had received no potassium chloride for at least twenty-four hours. In spontaneous attacks, which occurred during sleep, usually after a supper rich in carbohydrate, the changes were similar to those which followed the ingestion of glucose; there was more rapid reduction in venous than arterial potassium concentration, resulting in an increase in the arteriovenous difference. (Figs. 3, 4 and 5.) During the de-

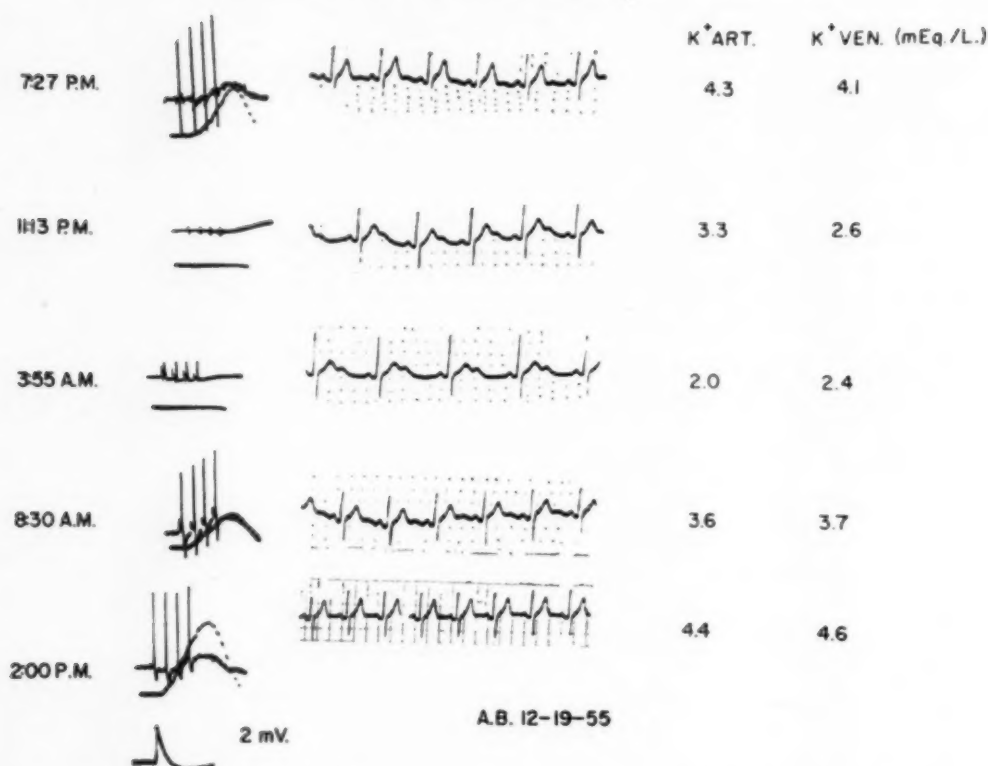


FIG. 4. Same as Figure 3, but illustrating the changes in muscle action potential (upper sweep) and tension (lower sweep) response to nerve stimulation, and changes in the electrocardiogram.

velopment of weakness following the ingestion of food or glucose, on fifteen occasions in three patients, the greatest arteriovenous potassium difference occurred early in the attack, approximately three hours after the meal, when only mild weakness was present, and when the mean arterial concentration was 4.14 mEq./L. and the venous 3.61 mEq./L. The reduction in venous potassium at this time was significant ($P < 0.01$), as was the change in arteriovenous difference from a mean of 0.02 ± 0.06 to 0.53 ± 0.08 mEq./L. ($P < 0.001$). In most instances the arteriovenous difference changed from an insignificant or negative value to a positive value, indicating uptake of potassium by the forearm. In the others, the arteriovenous difference merely became more positive, indicating either increased uptake of the ion by the forearm or a decrease in blood flow. The former seems more likely, in view of the further reduction in plasma potassium concentration that followed, and the lack of significant reduction in blood flow in the extremities of normal subjects during rest or sleep [15]. Occasionally, moderate weakness occurred while the plasma potassium concentration was still within the limits of normal, but with abnormally high arteriovenous difference.

As the plasma potassium concentration fell further and weakness became more pronounced the arteriovenous difference became smaller, although it remained positive, reflecting continued uptake of potassium by the extremity. During sleep both arterial and venous potassium concentrations fell more rapidly and weakness became more pronounced. (Fig. 3.) At the time of maximal weakness, six hours after the ingestion of supper or glucose, the plasma potassium concentration was at its lowest, the mean arterial concentration being 2.52 ± 0.20 mEq./L.; venous concentration, 2.21 ± 0.20 mEq./L.; and arteriovenous difference, 0.31 ± 0.07 mEq./L. The changes from the levels present prior to the attack were highly significant ($P < 0.001$, < 0.001 , and < 0.01).

After several hours of maximal weakness the venous potassium concentration began to rise slowly and soon exceeded the arterial concentration. Concurrently, there was a slight increase in strength. As the strength improved and activity increased, the venous potassium concentration and negative arteriovenous difference increased to a greater degree. Five hours after the time of maximal depression of plasma potassium concentration, the mean arterial concentration was

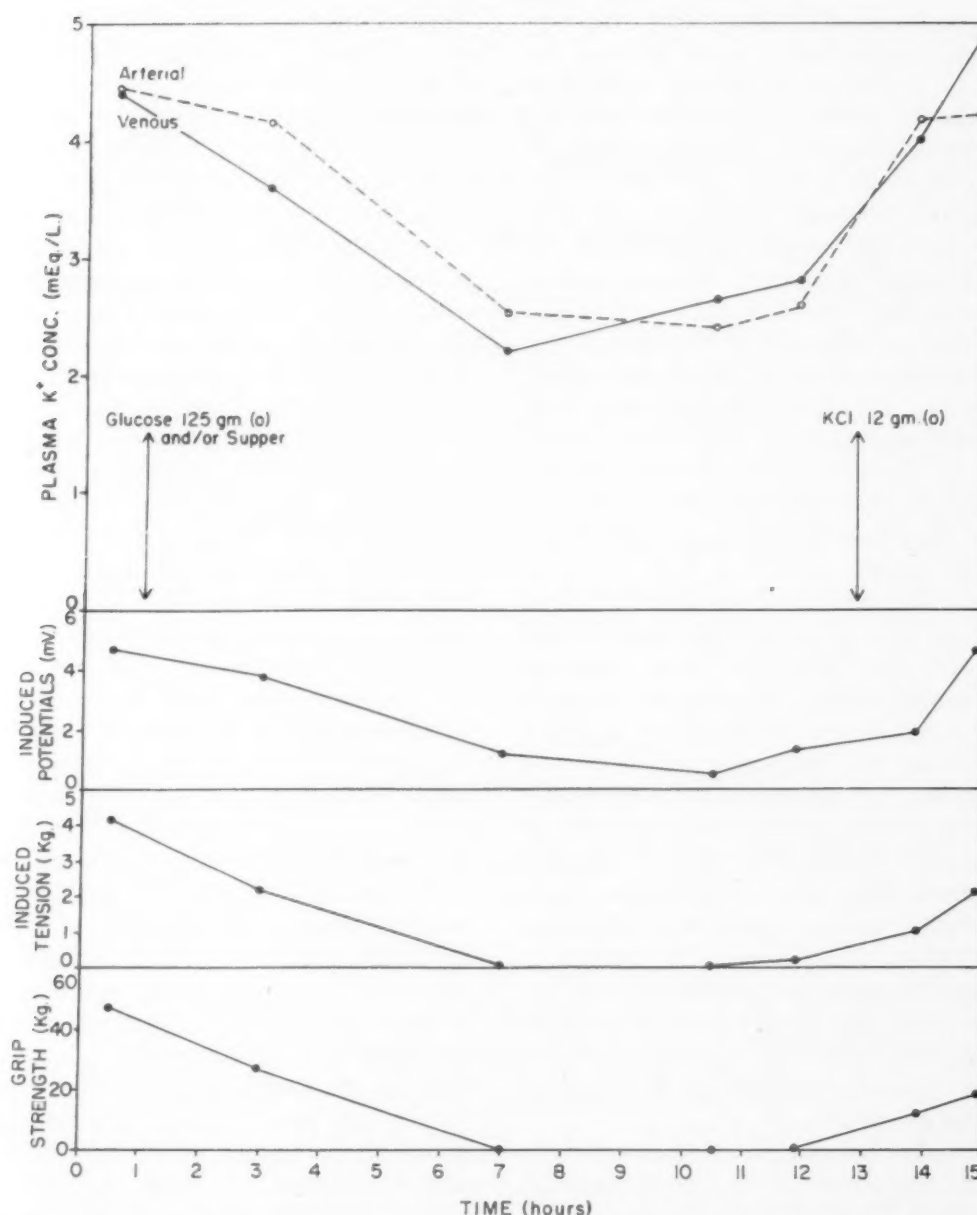


Fig. 5. Decrease in plasma potassium concentration (venous more than arterial) following supper and/or oral administration of glucose, marked reduction in grip strength and in the muscle action potential and tension response to nerve stimulation, and recovery following oral administration of potassium chloride. Average values are recorded for fifteen attacks in three patients.

2.42 ± 0.21 mEq./L.; venous concentration, 2.81 ± 0.25 mEq./L.; and arteriovenous difference, -0.39 ± 0.20 mEq./L. The change in arteriovenous difference from a positive to a negative value, which was significant ($P < 0.02$), indicated loss of potassium from the forearm.

During attacks of weakness, intermittent muscle contractions, although greatly reduced in force, resulted in four times as much increase in venous potassium concentration in the exer-

cised limb as prior to the attack. (Table I.) The increase was twice as great as that which occurred in normal subjects following much stronger muscle contractions [7]. The arteriovenous difference changed from a positive to a negative value, indicating loss of potassium from the forearm.

Effect of Potassium Chloride Administered during Attack. One hour after the oral administration of 9 to 12 gm. of potassium chloride (0.15 gm./kg.) during attacks of paralysis, generally

after slight spontaneous improvement, the rise in potassium concentration was greater in arterial plasma (mean increase 1.91 mEq./L.) than in venous (1.55 mEq./L.). (Figs. 3 and 5.) The arteriovenous potassium difference changed from a mean of -0.20 ± 0.18 to $+0.16 \pm 0.20$ mEq./L., which was not significant. At this time there was only slight improvement in strength. During the next hour the venous concentration increased more rapidly than the arterial, so that at the end of two hours the increase in potassium concentration was greater in venous plasma (mean increase 2.43 mEq./L.) than in arterial plasma (1.95 mEq./L.). (Table 1 and Figs. 1, 3, and 5.) The former was the same as in normal subjects while the latter was significantly less. The arteriovenous difference changed from a mean of 0.16 ± 0.20 mEq./L. at the end of the first hour to -0.67 ± 0.18 mEq./L. at the end of the second hour, which was significant ($P < 0.02$). In most instances the arteriovenous difference changed from a positive or insignificant value to a negative value, indicating loss of potassium from the forearm. In a few, the difference merely became more negative, indicating either increased loss of the ion from the forearm or a decrease in blood flow. The former seems more likely, as there is no reason to believe that the ingestion of potassium chloride decreases blood flow. The change in arteriovenous difference was significantly different from that which occurred in normal subjects (Table 1), in whom administration of potassium chloride was followed by evidence of uptake of the ion by the extremity.

Two hours after the administration of potassium chloride, intermittent muscle contractions resulted in three times as much increase in venous potassium concentration as occurred prior to the attack.

MUSCLE STRENGTH

When not in an attack and at their best strength, two of the three patients had normal strength; the third exhibited mild weakness.

During an attack there was characteristic progression of weakness. This began three to five hours after a high carbohydrate supper (in three of twelve trials) or after the oral administration of 125 gm. of glucose (in twelve of twenty trials), and one-half to one hour after the intra-arterial injection of insulin (in each of two trials) or epinephrine (in each of two trials). The muscles of the extremities were the first to be

affected, followed by those of the trunk and neck. At the onset of weakness there was invariably reduction in the venous concentration of potassium, less marked reduction in arterial concentration, and increase in the arteriovenous difference. (Fig. 5.) During the following two to five hours there was progressive increase in weakness, concomitant with further reduction in plasma potassium concentration, and continued positive arteriovenous difference. These changes were accelerated by rest and retarded by activity. The effect of sleep was greater than that of enforced daytime rest, presumably owing to better muscle relaxation, but attacks of severe weakness could be precipitated during the day. When one arm was kept at enforced rest it became weaker more rapidly than the opposite extremity. Local exercise resulted in local improvement in strength, and general exercise could abort a mild attack of weakness.

Maximum weakness occurred five to eight hours after supper, three to six hours after the administration of oral glucose, and two to five hours after administration of insulin or epinephrine. Following intra-arterial injection of the latter drugs the weakness of the injected arm was the same as that of the opposite extremity.

In ten of the nineteen attacks which were studied there was virtually complete flaccid paralysis of the extremities, marked weakness of the neck and trunk, and disappearance of the tendon reflexes and of muscle contraction in response to direct percussion. In the remaining attacks the weakness of these muscles was moderately severe. There was only mild impairment of swallowing, speech, breathing, and of the facial muscles, except for three attacks in which there was moderate difficulty in swallowing and breathing. The extraocular muscles were not affected.

In most instances slight improvement in strength occurred after one to five hours of maximal weakness. This was increased if the patient was strong enough to move about or exercise, but movement was usually very limited until potassium chloride was administered. Following the administration of 0.15 gm./kg. orally, improvement in strength occurred slowly, beginning in one-half to one hour, becoming appreciable in two to three hours, and maximal in three to five hours. (Fig. 5.) The improvement in strength lagged behind the increase in plasma concentration of potassium, and became more rapid coincident with the increase in the venous

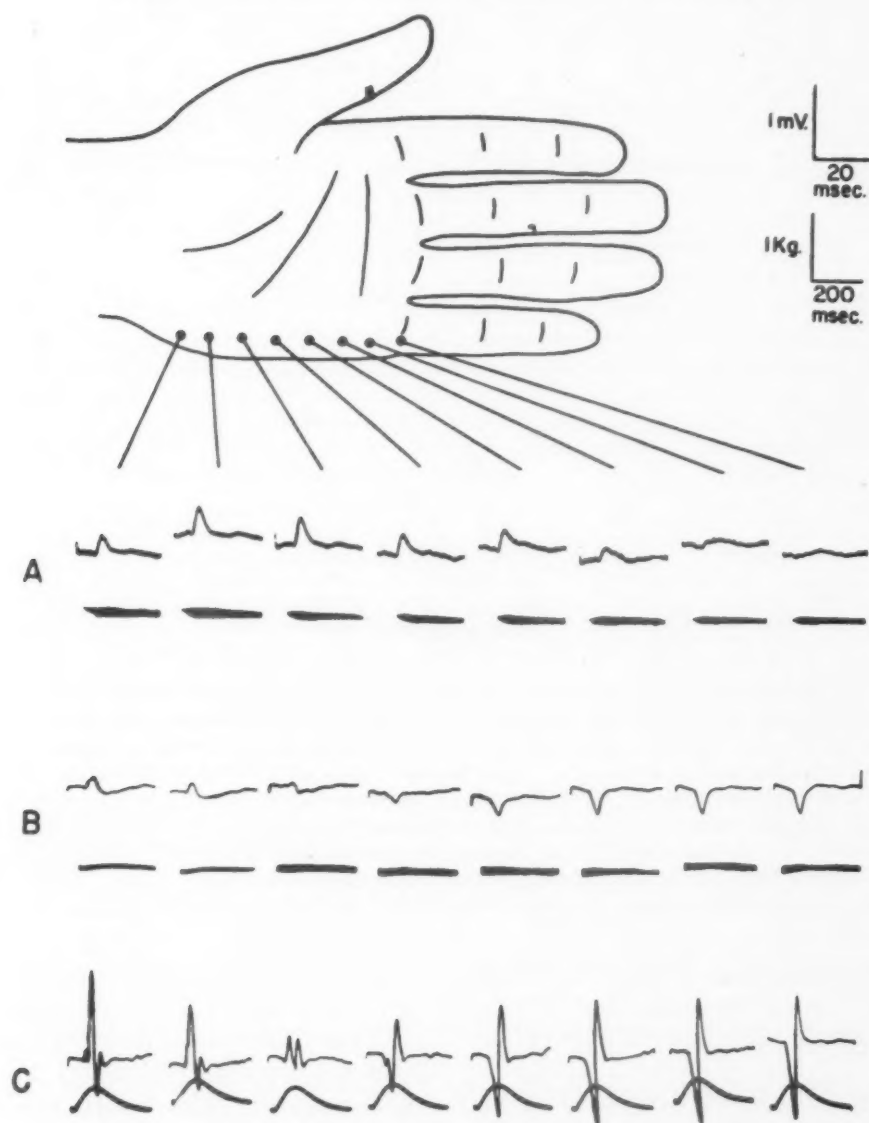


FIG. 6. A, failure of propagation of the muscle action potential response to nerve stimulation during an attack of weakness. (M. H., February 4, 1955.) The muscle action potential (upper sweep) cannot be recorded several centimeters distal to the region in which the motor end-plates are believed to be concentrated (under the proximal three electrodes). The action potentials recorded from each electrode are identical in form and latency, and differ only in amplitude, which diminishes away from the end-plate region. The mechanical response (lower sweep) is so weak that it cannot be recorded. B, beginning recovery of propagation of the muscle action potential, one hour after oral administration of potassium chloride. In the end-plate region the action potentials have an initial upward (negative) deflection, representing depolarization arising in this region. Distally, the action potentials have an initial downward (positive) deflection, caused by the approaching wave of depolarization, in relation to which the distal region is relatively positive. Propagation has not recovered sufficiently for this wave to reach the distal electrodes, so that the downward deflection is not followed by an upward deflection signalling arrival of the wave of depolarization. C, complete recovery of propagation of the muscle action potential, and increase in amplitude of the potential and of the mechanical response, two hours after potassium chloride. Distal to the end-plate region, the initial downward deflection of the action potential is now followed by an upward deflection as the negative wave of depolarization reaches each electrode. The latent period between stimulus artifact and depolarization (upward deflection) increases away from the end-plate region.

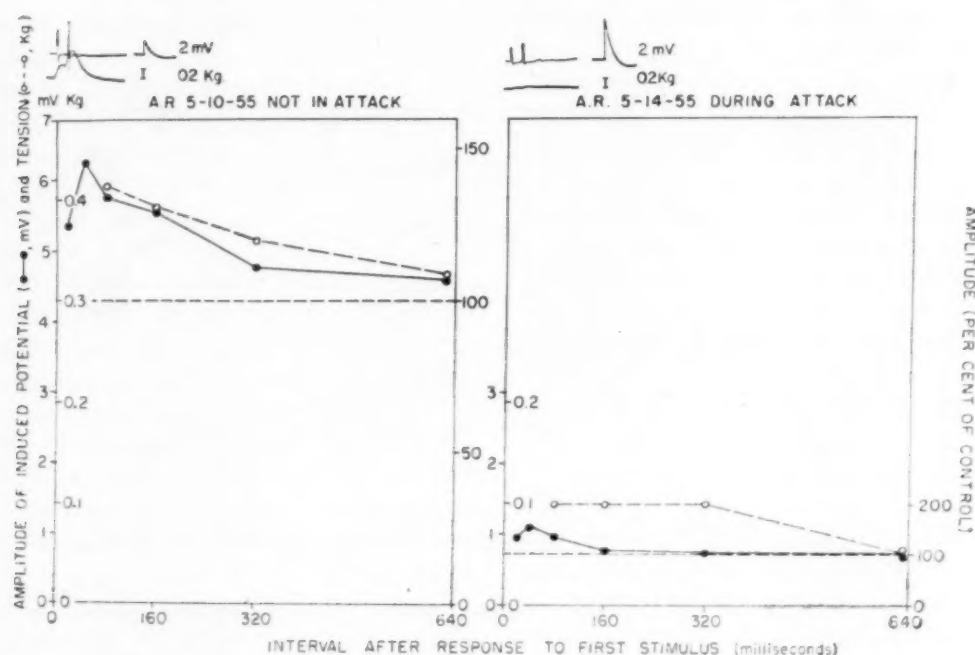


FIG. 7. Left, time course of the increase in the muscle action potential (●—●) and tension (○—○) response to a single test stimulus applied at different intervals after the response to an initial stimulus. The amplitude of the action potential and tension response to the initial stimulus is indicated by the broken line drawn at 100 per cent. Patient not in attack. Right, time course of the increase in response to the second stimulus during an attack. The per cent increase in the tension response is greater, despite the weakness of the response. Prior to the attack a weak contraction was not followed by potentiation of a second contraction. At the top are shown the muscle action potential (upper sweep) and tension (lower sweep) response to two stimuli eighty milliseconds apart.

concentration of potassium above the arterial which occurred during the second and third hours after potassium chloride administration.

MUSCLE RESPONSE TO A SINGLE NERVE STIMULUS

When Not in Attack. The muscle action potential and tension evoked by nerve stimulation were at the lower limits of the normal range, and the mean responses were one-half the normal means. The action potential was propagated in normal fashion from the region of the motor end-plates. As in normal subjects, reduction in the intensity of nerve stimulation resulted in equal diminution in these responses, without failure of propagation of the muscle action potential.

During Attack. The muscle response to nerve stimulation was progressively reduced. (Figs. 3, 4 and 5.) The evoked tension and the strength, declined more rapidly than the evoked muscle action potential. (Fig. 5.) During some attacks no tension response could be elicited and there was complete paralysis of the extremity, despite reduction of the action potential by only 60 per cent. (Fig. 9.) Propagation of the muscle action

potential across the muscle was also decreased, and in severe attacks no potential could be recorded several centimeters from the region in which the motor end-plates are believed to be concentrated. (Fig. 6.) In the most severe attacks the muscle action potential was also reduced to near zero even in the end-plate region. (Figs. 4 and 6.)

During Recovery. The muscle action potential and propagation of this potential returned toward normal more rapidly than the tension response or strength (Figs. 5 and 6), but all returned to the control values several hours after administration of potassium chloride. The tension response sometimes increased further and exceeded that which was present prior to the attack. (Fig. 4.) This was not accompanied by repetitive firing of the action potential.

EFFECT OF MUSCLE ACTIVITY ON MUSCLE RESPONSE TO NERVE STIMULATION

When Not in Attack. Increased response following a single muscle contraction: Following a single nerve stimulus and muscle response there was an increase in amplitude of the response to a second

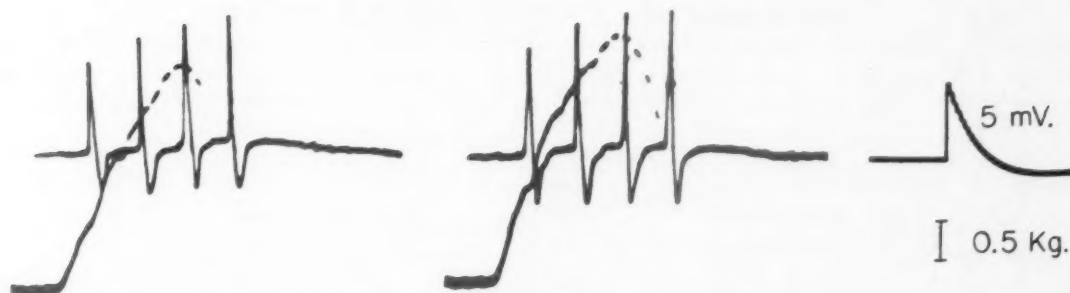


FIG. 8. Progressive increase in the muscle action potential (upper sweep) and tension (lower sweep) response to nerve stimulation as a result of prior nerve stimulation and muscle contraction. (A. R., May 18, 1955.) Left, response to a train of four nerve stimuli (forty milliseconds apart) showing facilitation of the muscle action potential. Right, increased response to a train of four nerve stimuli, forty milliseconds apart, after repeated muscle contractions evoked by delivery of this train every five seconds for one minute. Facilitation is still present.

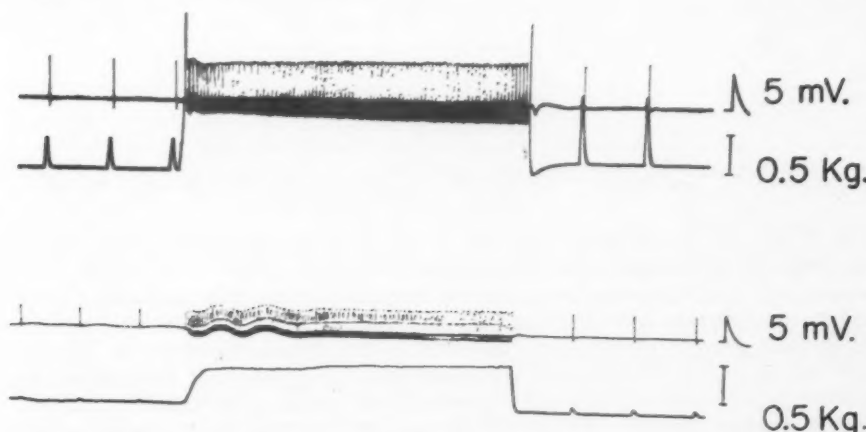


FIG. 9. Post-tetanic potentiation. Above, increase in tension (lower sweep) and action potential (upper sweep) response of muscle to a supramaximal nerve stimulus delivered every two seconds following tetanic contraction (4 kg., sweep off film) evoked by supramaximal nerve stimulation at 25 per sec. for ten seconds. Patient not in attack. (M. H., January 19, 1955.) Below: during an attack. The per cent increase in tension response is greater, even though the tetanic contraction is only one-tenth as strong. (M. H., January 9, 1955.)

stimulus delivered within sixteen milliseconds to one second. (Fig. 7.) The tension was increased to a slightly greater extent than the muscle action potential. The maximum increase in the action potential occurred when the two stimuli were forty milliseconds apart, and, in the tension, eighty milliseconds (the smallest interval at which the tension responses were discrete). At these intervals the increases in amplitude of action potential and tension were 40 and 50 per cent in one patient, and 10 and 25 per cent in the other two patients.

In normal subjects there was no change in amplitude of the muscle response to a nerve stimulus which was delivered at similar intervals following an initial muscle contraction [7,16].

Increased response during repeated or tetanic muscle contraction: Repeated muscle contractions evoked

by intermittent nerve stimulation (train of four stimuli, forty milliseconds apart, repeated every two and one-half to ten seconds for one-half to two minutes) resulted in a progressive increase in amplitude of the muscle action potentials and tension, by up to 50 per cent. (Fig. 8.) During tetanic muscle contraction evoked by repetitive nerve stimulation at frequencies of 1 to 50 per second for up to ten seconds there was a similar increase. (Fig. 9.)

In normal subjects there was no change in amplitude of muscle response during intermittent nerve stimulation, no change or a slight increase during repetitive nerve stimulation at frequencies up to 25 per sec., and a progressive decline during stimulation at 50 per sec. [7,16].

Increased response following tetanic muscular contraction (post-tetanic potentiation): Half a second

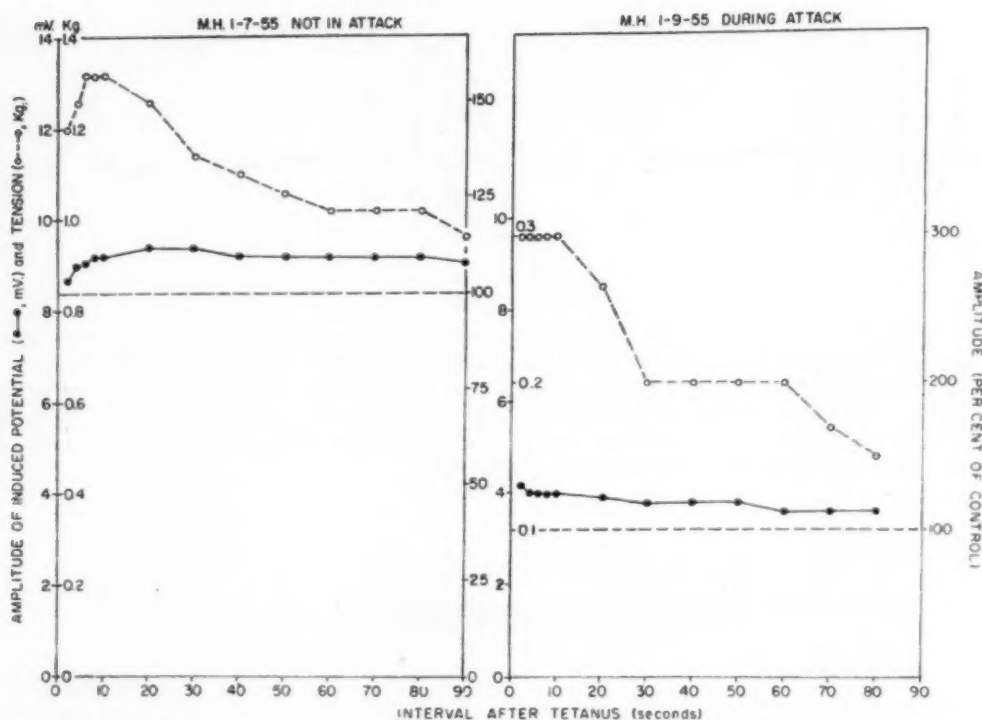


Fig. 10. Left, time course of the increase in muscle action potential (●—●) and tension (○—○) response to a single supramaximal nerve stimulus delivered at varying intervals after tetanic muscle contraction evoked by supramaximal nerve stimulation at 25 per second for ten seconds. The amplitude of the tension and action potential response to a single stimulus prior to the tetanus is indicated by the broken line drawn at 100 per cent. Patient not in attack. Right, increased post-tetanic potentiation of the tension response to a single supramaximal nerve stimulus during an attack, as indicated by the per cent change in tension response. This occurred even though the tension responses to single and tetanic stimulation were reduced to approximately one-tenth the original amplitude.

after tetanic muscular contraction evoked by repetitive nerve stimulation at a frequency of 10 to 200 per second for one-fifth of a second to two minutes, or after maximal voluntary contraction, there was an increase in the response to a single nerve stimulus. (Fig. 9.) This increase became maximal two to six seconds after the repetitive stimulation or maximal voluntary contraction and lasted for three to five minutes. (Fig. 10.) The tension response was increased by a mean of 71 and 79 per cent, and the muscle action potential by a mean of 10 and 8 per cent. (Table II.) The degree of post-tetanic potentiation was less following nerve stimulation at such high frequency that the resulting muscle contraction was not sustained, for example at 200 per second, and it was less following repeated tetanic contractions.

In normal subjects there was similar post-tetanic potentiation of the mechanical response to a nerve stimulus, but the muscle action potential was unchanged [7].

During Attack. As long as a muscle twitch

could be elicited, the per cent increase in response of the muscle during and following paired (Fig. 7) or repetitive nerve stimulation (Figs. 9 and 10), or following maximal voluntary contraction, was greater than prior to the attack. When the tension response to single or tetanic nerve stimulation was reduced to one-tenth of the original force, it was increased after a tetanus by a mean of 200 per cent, and the action potential was increased by a mean of 25 per cent. (Table II.) These changes were significantly greater than those which occurred prior to the attack or those in normal subjects ($P < 0.001$ and < 0.01). When the attack became so severe that no tension was elicited, there was no increase in tension or action potential response after tetanic nerve stimulation, even though this evoked action potentials of appreciable size.

In normal subjects tetanic contraction of less than one-third maximal amplitude, evoked by submaximal stimulation, was followed by only slight potentiation of the tension response, and no potentiation of the action potential [7].

TABLE II
MUSCLE ACTION POTENTIAL AND TENSION RESPONSE TO A SINGLE NERVE STIMULUS BEFORE AND FOUR SECONDS AFTER TETANIC OR MAXIMAL VOLUNTARY CONTRACTION, LASTING TEN SECONDS

Data	Not in Attack			In Attack		
	Number of Studies in Three Patients	Muscle Action Potential (mV.)	Tension (kg.)	Number of Studies in Three Patients	Muscle Action Potential (mV.)	Tension (kg.)
Before tetanic contraction.....	15	7.5 ± 0.2	0.5 ± 0.1	3	3.2 ± 0	0.1 ± 0
After.....		8.2 ± 0.2	0.8 ± 0.1		4.0 ± 0.1	0.2 ± 0
Per cent increase.....		10 ± 2	71 ± 21		25 ± 3	200 ± 0
P.....		<0.001	<0.01		<0.02	<0.001
Before maximal voluntary contraction.....	4	6.1 ± 0.1	0.5 ± 0.05			
After.....		6.6 ± 0	0.9 ± 0.01			
Per cent increase.....		8 ± 0.7	79 ± 42			
P.....		<0.01	>0.1			

NOTE: Mean values ± S.E. of mean. Tetanic contraction elicited by nerve stimulation at 25 per second.

During Recovery. Following administration of potassium chloride and improvement in muscle response, the increase in response during and following paired or repetitive nerve stimulation, or following maximal voluntary contraction, continued to be greater than when the patient was not in an attack.

EASE OF DEPOLARIZATION BY ACh OR OTHER DEPOLARIZING COMPOUNDS

When Not in Attack. There was no difference between the patients studied and normal subjects [17,18] in the ease of depolarization of muscle by either intra-arterially injected ACh (1 to 10 mg.), neostigmine (0.1 to 1 mg.), choline (15 mg.) or decamethonium (0.05 mg.), as indicated by the depressant effect of these compounds on the muscle action potentials and tension evoked by nerve stimulation.

During Attack. Resistance to depolarization developed, particularly by ACh. The "prompt" depressant effect of this compound on the muscle action potentials and tension evoked by nerve stimulation was markedly inhibited concomitant with the reduction in amplitude of the potentials and tension. (Fig. 3.) These were amplified in recording in order to maintain accuracy of measurement. The depressant effect of neostigmine on evoked muscle potentials and tension was reduced and delayed. (Fig. 11.) The depressant effect of choline and of decamethonium was delayed, but only slightly reduced. At no time

did ACh or any of the other depolarizing compounds produce an increase in amplitude of evoked muscle potentials or tension. Thus, these compounds did not reverse the defect in muscle function that was present during the attack.

During Recovery. Following spontaneous improvement, or administration of potassium chloride, the resistance to depolarization disappeared, as indicated by return of the prompt depressant effect of ACh and of choline. This occurred more rapidly than recovery of the evoked muscle potentials, and much more rapidly than recovery of muscle tension and strength. Two to three hours after the ingestion of potassium chloride the prompt depressant effect of ACh and choline became greater than it was prior to the attack, indicating an increase above normal in ease of depolarization. (Fig. 3.)

INFLUENCE OF CORTISONE ON DEVELOPMENT OF WEAKNESS

The daily administration of 200 mg. of cortisone orally for three or more days prevented induction of an attack by an evening meal which was high in carbohydrate, and which was followed by oral glucose, in two patients on each of six days. During this time sodium chloride intake was restricted to 4 gm. a day but potassium chloride was not administered. Sodium chloride restriction had no influence prior to cortisone administration, when a severe attack of weakness was induced by a similar evening meal

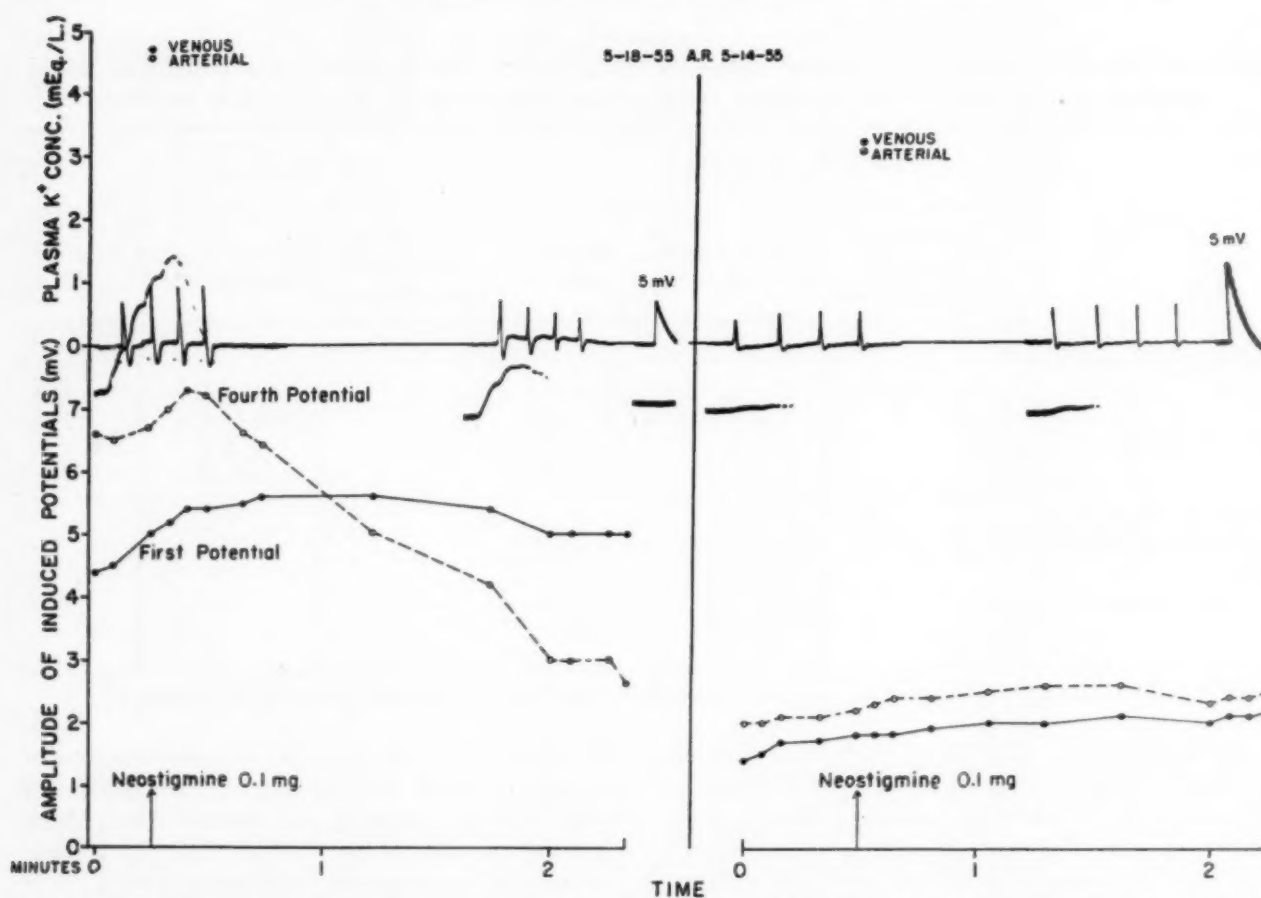


FIG. 11. Left, plasma potassium concentration, muscle action potential (upper sweep) and tension (lower sweep) response to four nerve stimuli (forty milliseconds apart) and depressant effect of intra-arterial neostigmine on this response, when the patient was not in an attack. The amplitude of the first (●—●) and fourth (○—○) muscle action potentials in response to a train of four nerve stimuli (forty milliseconds apart) evoked every five seconds has been plotted below. Right, decrease in plasma potassium concentration, in muscle action potential and tension response to nerve stimulation, and in depressant effect of neostigmine on this response, during an attack.

followed by oral glucose in fourteen of seventeen trials.

ELECTROCARDIOGRAPHIC CHANGES

Following the administration of food, glucose, insulin or epinephrine, the characteristic electrocardiographic changes of hypokalemia began at the same arterial potassium concentration as in normal subjects, 3.3 mEq./L. As in normal subjects the first change to appear was the positive after-potential, followed by prolongation of the PR, QRS and QT intervals and lowering of the T wave. (Fig. 4.) With further reduction in arterial potassium concentration the changes became more pronounced but were much less severe than the concomitant alterations in evoked muscle action potentials. The electrocardiographic changes were moderately greater than those seen in normal subjects following the induction of comparable degrees of hypokalemia,

but the difference was much less than in the case of skeletal muscle. Following the administration of potassium chloride the electrocardiogram returned to normal, concomitant with the improvement in skeletal muscle function. This was followed by peaking and elevation of the T waves above the initial level.

COMMENTS

Movement of Potassium. In three patients with periodic paralysis, attacks of weakness, whether "spontaneous" or induced, were invariably associated with reduced plasma potassium concentration and abnormally high arteriovenous difference, indicating abnormal uptake of the ion by the forearm. Glucose, which caused uptake of potassium by the forearm in normal subjects, produced more marked reduction in venous potassium concentration in these patients, probably owing to more marked uptake of

the ion by muscle. Epinephrine may also have produced greater uptake than in normal subjects but the difference was less striking. Insulin, which caused loss of potassium from the forearm in normal subjects and entry into some other site, caused uptake of potassium in the patient studied.

Since muscle constitutes the greatest part of metabolically active tissue in the forearm, movement of potassium into or out of the extremity was ascribed to changes in the concentration or content of potassium in the muscle cells. Movement of water was not studied, nor was direct analysis of muscle performed, so that changes in concentration and content could not be differentiated. Direct analysis of muscle has recently been reported in one patient [6]. The limited data indicated an increase in intracellular water and potassium content during an attack of periodic paralysis, without change in concentration.

Mild attacks of weakness were frequently present when the plasma potassium had fallen to only low normal levels, but there was always a positive arteriovenous difference in the forearm. Slow uptake of potassium by muscle may account for reported attacks of periodic paralysis which were unaccompanied by reduction in plasma potassium concentration, but which were relieved by administration of potassium chloride [7,8,19]. It would not account for the rare occurrence of familial periodic paralysis in which attacks are not relieved by potassium [20]; this disorder appears to have a different etiology.

Rest accelerated the reduction in plasma potassium and progression of weakness, probably by aiding the uptake of potassium by muscle. Exercise had the opposite effect. During attacks, as well as during recovery, muscle contraction resulted in a greatly increased output of potassium from muscle, probably owing to abnormally high intracellular concentration or content of the ion. In normal subjects heightened output was observed after the administration of potassium chloride, which is believed to increase the intramuscular concentration or content of the ion [7]. It is possible that there is increased permeability of the cell membrane to the exit of potassium during attacks of paralysis, but no such abnormality was present prior to the attack when muscle contraction resulted in less output of the ion than in normal subjects. In contrast, there appeared to be increased ease of entry, or uptake, of potassium both before and during the development of paralysis.

Spontaneous recovery was associated with evidence of slow loss of potassium from muscle, and both were increased by muscular activity. After the administration of potassium chloride there was an increase in plasma potassium concentration, without evidence of movement of potassium into or out of muscle during the first hour. This was followed by slight improvement in strength. The ensuing increase in muscular activity was accompanied by, and may have been responsible for, the marked loss of potassium from muscle which then occurred. This, in turn, was followed by, and was probably responsible for, more rapid improvement in strength.

The cellular transport of potassium ions is frequently associated with reciprocal exchange of sodium ions [27], but no changes in plasma concentration of sodium were detected which were greater than the error of the analytic procedure. Reciprocal transfers of sodium and potassium between the intracellular and extracellular compartments during an attack of paralysis, and following recovery, have been described in one patient [5].

The action of cortisone in protecting against the induction of attacks of periodic paralysis provides an additional tool for study of the disease. However, the hormone does not seem to have any advantage over the prophylactic administration of potassium chloride in clinical management, particularly since prolonged use increases urinary excretion of potassium and must be supplemented by daily ingestion of the ion.

Muscle Function. During attacks of periodic paralysis there were at least three abnormalities of muscle function: (1) reduction in responsiveness to nerve stimulation; (2) reduction in spread of the excitation wave along the muscle fiber; and (3) reduction in contractility.

Reduced responsiveness was manifested by diminution in amplitude of muscle action potentials evoked by nerve stimulation. It was accompanied by a decrease in the depolarizing action of injected ACh, and therefore may be due, at least in part, to resistance to the action of ACh released from the motor nerve endings. Similar changes occur in the experimental animal following application to the motor end-plate region of an anodal current, which produces an increase in the resting membrane potential above the normal level (hyperpolarization) [22]. An increase in the resting membrane potential has also been observed in the experimental

animal following increase in the ratio of intracellular to extracellular concentration of potassium [23]. It is likely that a similar change occurs during attacks of periodic paralysis, and that this hyperpolarization is responsible for decreased responsiveness of the muscle to nerve stimulation and to the depolarization action of ACh. The action of ACh is specific for the motor end-plates [24], so that, while reduction in amplitude of the muscle action potentials in the end-plate region can be ascribed to hyperpolarization in this region, reduction in spread of the excitation wave indicates that there is resistance to depolarization in other parts of the muscle fiber as well. It is probable that the entire muscle membrane is hyperpolarized.

Decreased force of muscle contraction developed more rapidly during attacks of paralysis, and was generally more striking than the concomitant reduction in amplitude and propagation of the muscle action potentials. A defect in the contractile mechanism may therefore be the most important of the changes in muscle function. This defect, too, may be due in part to hyperpolarization of the muscle membrane, since a high membrane potential is said to keep actomyosin in an uncontracted state [25]. It may also be due to increased intracellular concentration of potassium, which is also reported to reduce contractility of actomyosin [26].

The weakness of periodic paralysis appears to be due to the following sequence: (1) abnormal uptake of potassium by muscle; (2) marked increase in the intracellular to extracellular concentration ratio of this ion; (3) hyperpolarization of the muscle membrane; and (4) reduction in muscle responsiveness to nerve stimulation, in propagation of excitation, and in contractility. It is not known whether the abnormal uptake of potassium by muscle resulted in increased intracellular concentration of the ion, or in increased content without change in concentration. If the changes in muscle function were due to an increase in the intracellular to extracellular concentration ratio of potassium, it seems likely that there was an increase in intracellular concentration, since weakness in periodic paralysis is more frequent and severe than in other disorders associated with hypokalemia, and occurs at lesser degrees of hypokalemia. In other disorders in which there is reduced plasma potassium concentration, whether due to excessive loss or deficient uptake of potassium [27], or to administration of insulin

[28] or adrenal cortical hormones [29], there is either no change or a decrease in the intracellular concentration of the ion, so that any increase in concentration ratio is due to the hypokalemia alone. An increase in the intracellular concentration of potassium during attacks of periodic paralysis would result in a more marked change in concentration ratio and in muscle function. In order for the intracellular concentration (or content) to increase significantly, it is evident that there would have to be a shift to muscle of potassium from other tissues, since the total extracellular content of the ion is normally less than 2 per cent of that in muscle, and cannot alone significantly affect the latter. An increase in the potassium content of muscle by 39 per cent during an attack of periodic paralysis has been reported [6]. It is not known if a change in intracellular content of potassium may affect membrane potential and function of muscle in the absence of a change in intracellular concentration.

Weakness due to periodic paralysis was reversed by muscle activity or administration of potassium, probably as a result of decrease in the intracellular concentration or content of potassium, in the concentration ratio of this ion, and in the membrane potential. Both procedures resulted in a striking loss of potassium from muscle. Two to three hours after the administration of potassium chloride and shortly after the loss of potassium from muscle which accompanied return of muscular activity, there was evidence of transient decrease in the membrane potential below normal. The depolarizing action of injected ACh or choline exceeded that observed prior to the attack, probably owing to temporary decrease in the concentration ratio of potassium below normal. A similar change occurred following the administration of potassium chloride to normal subjects [7]. It resembles the effect of application of a cathodal current to the end-plate region [22].

The effect of motor activity in retarding the onset of weakness and accelerating recovery may account for the relative resistance of the muscles of respiration during attacks of paralysis. It is of interest that when weakness occurs in severe hypokalemia due to other causes the muscles of respiration may be affected at the same time as the peripheral muscles [28], presumably because the increased potassium ratio is due to hypokalemia alone.

Muscle activity resulted in improvement in

function even when patients were not in an attack. This suggests that there may be some increase in the intracellular concentration of potassium, concentration ratio and membrane potential at that time, even though muscle contraction did not result in abnormal output of the ion. Both single and tetanic muscle contractions produced an increase in the muscle action potential and tension response to nerve stimulation, whereas in normal subjects a single muscle contraction was not followed by any change in response, and tetanic contraction was followed by potentiation of the tension, but not of the muscle action potential [1]. It could not be ascertained whether the increase in muscle action potential response was due to improvement in propagation of the action potential along each muscle fiber, or to an increase in the number of fibers excited by nerve stimulation.

During attacks of weakness muscle contraction was followed by greater post-tetanic potentiation of muscle action potential and tension, and more output of potassium from the muscle, than occurred prior to the attack or in normal subjects. This took place even though muscle contraction was greatly reduced in force, to levels at which no potentiation or potassium release occurred prior to the attack or in normal subjects. However, when the attack became so severe that no tension was elicited on nerve stimulation there was no increase in the action potential or tension response, even after prolonged repetitive nerve stimulation which evoked muscle action potentials. Therefore, the effect of muscle activity in improving action potential and tension response in periodic paralysis is a postjunctional (muscle fiber) phenomenon, as in normal subjects [1], and is probably due to muscle contraction and resulting release of potassium.

Although the reduced responsiveness of muscle to nerve stimulation which occurred during attacks of weakness was associated with resistance to the depolarizing action of ACh, it was not made worse by repetitive nerve stimulation, or ameliorated by the administration of ACh or neostigmine. In this regard, the defect resembles that which is produced by application of an anodal current [22], and differs from the neuromuscular block which is produced by curare in normal subjects [18] and from that which is present in patients with myasthenia gravis [30]. The latter are attributable primarily to resistance to the action of ACh on the motor end-plates. In

partially curarized animals [37] or man [18], and in patients with myasthenia gravis [30], an increase in muscle action potential response to nerve stimulation occurs following a conditioning stimulus or tetanus, but the properties, and probably the mechanism, of this facilitation differ from those seen in patients with periodic paralysis. In curare block and in myasthenia gravis the facilitation has a much shorter time course, and is attributable to increased release of ACh from the motor nerve endings. It is prejunctional (nerve ending) in origin, since it is pronounced even after repetitive nerve stimulation at a frequency so rapid that muscle contraction is not maintained [16,18]. In patients with periodic paralysis this does not occur, providing additional evidence that post-tetanic potentiation in this disease is postjunctional, and attributable to muscle contraction and resulting release of potassium.

Cardiac Function. The electrocardiographic changes which occur during hypokalemia in normal subjects and in patients with periodic paralysis indicate that there is resistance to depolarization and repolarization of cardiac muscle, particularly the latter. The earliest change, the positive after potential, has been studied in detail [32]. While there was no precise correlation between the degree of electrocardiographic changes and of hypokalemia, the changes were moderately greater in patients with familial periodic paralysis than in normal subjects at comparable plasma levels [1]. However, the difference was far less than in the case of skeletal muscle function. It is possible that the concentration ratio of potassium may be less important in cardiac muscle function than the extracellular concentration, in contrast to skeletal muscle. Study of this problem in experimental animals has yielded conflicting results [33,34]. It seems more likely that the concentration ratio is important, but may not be as high in cardiac as in skeletal muscle during attacks of periodic paralysis, owing to the continual activity of cardiac muscle, which normally has a lower concentration of potassium [35].

SUMMARY

Study in two patients with familial periodic paralysis and in one with non-familial periodic paralysis of potassium movement and associated changes in muscle function yielded the following results:

1. The administration of glucose produced a greater fall in venous potassium concentration in these patients than in normal subjects, probably owing to greater uptake of the ion by muscle.

2. The administration of epinephrine may have produced greater uptake of potassium by muscle in these patients than in normal subjects, but the difference was less marked than in the case of glucose.

3. The administration of insulin resulted in evidence of movement of potassium into muscle, in contrast to movement out of muscle in normal subjects.

4. Attacks of weakness which occurred spontaneously or following the administration of food, glucose or insulin were associated with reduced plasma potassium concentration and abnormally high arteriovenous difference, indicating abnormal uptake of the ion by muscle, and with reduction in muscle responsiveness to nerve stimulation and acetylcholine, in propagation of excitation, and in contractility.

5. In these patients muscle contraction during attacks, even though very weak, caused more loss of potassium from muscle and greater increase in muscle responsiveness and contractility than prior to the attack, or than in normal subjects.

6. Spontaneous recovery from weakness was associated with leakage of potassium from muscle, and was accelerated by exercise. During recovery following the administration of potassium chloride there was, first, slight improvement in strength which was followed by loss of potassium from muscle, and then more rapid improvement.

7. The weakness of periodic paralysis appears to be due to the following sequence: (1) abnormal uptake of potassium by muscle; (2) marked increase in the intracellular to extracellular concentration ratio of this ion; (3) hyperpolarization of the muscle membrane; and (4) reduction in muscle responsiveness to nerve stimulation, in propagation of excitation, and in contractility.

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The Electrocardiogram and Potassium Metabolism*

Electrocardiographic Abnormalities in Primary Aldosteronism and Familial Periodic Paralysis

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THAT disturbances in potassium metabolism may give rise to electrocardiographic abnormalities has been known for some time. The present publication aims to elucidate this

dilated. The ocular fundi showed bilateral papilledema with contracted vessels. The daily urine production was 2,500–5,000 ml., the specific gravity was 1.001–1.004 (maximally 1.016), urea clearance was

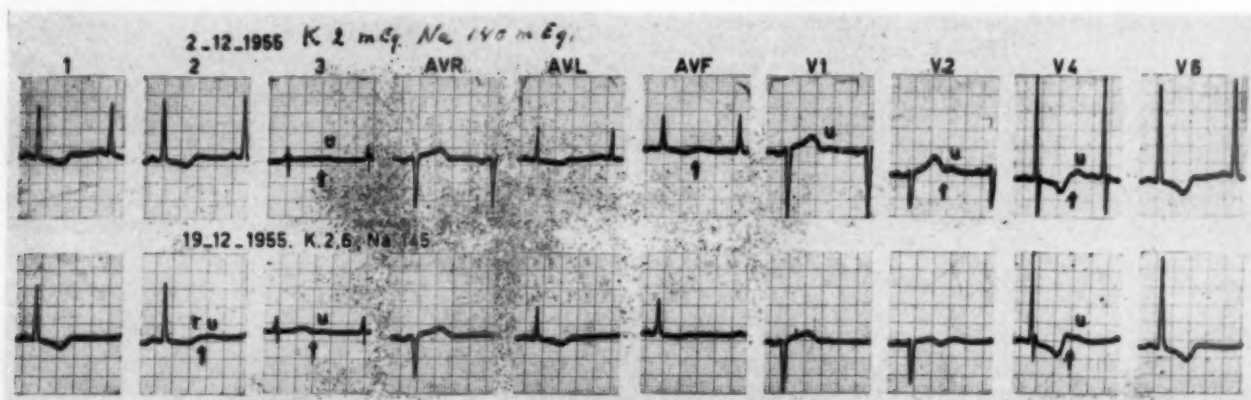


FIG. 1. Primary aldosteronism; preoperative electrocardiograms with serum potassium and serum sodium levels.

correlation by comparing the abnormalities occurring in primary aldosteronism with those observed in familial periodic paralysis, two widely divergent disturbances of potassium metabolism. In addition it is hoped that the data will throw some light on the relationship between the electrocardiographic abnormalities and muscular paralysis in general. The importance of this has been stressed by Tarail [1].

The Electrocardiogram in Primary Aldosteronism. The clinical data on this patient will be presented only briefly; a more extensive review may be found in another publication [2].

This seventeen year old boy had suffered from polyuria and polydipsia since early childhood. He had no muscle weakness or myopareses. The blood pressure was markedly increased (195/125–220/150 mm. Hg). The brachial artery was palpable and the aorta

120 per cent and the phenolsulfonphthalein 80 per cent. The potassium serum was 1.7 to 2.8, serum sodium, 143 to 150; serum chloride, 100 mEq./L.; the serum calcium, 9.9 mg. per cent; alkali reserve, 57 volumes per cent, pH 7.44. We are indebted to Dr. A. Wettstein of Basle for determination of the aldosterone excretion. This was clearly increased: 34 μ g./twenty-four hours. Cardiac catheterization yielded the following results:

	Pressure (mm. Hg)	O ₂ Saturation (%)
Right atrium.....	0	72.5
Right ventricle.....	38/0
Pulmonary artery trunk...	35/10	71.3
Pulmonary "capillaries"...	10	99.3

* From the Department of Internal Medicine, State University of Groningen, The Netherlands.

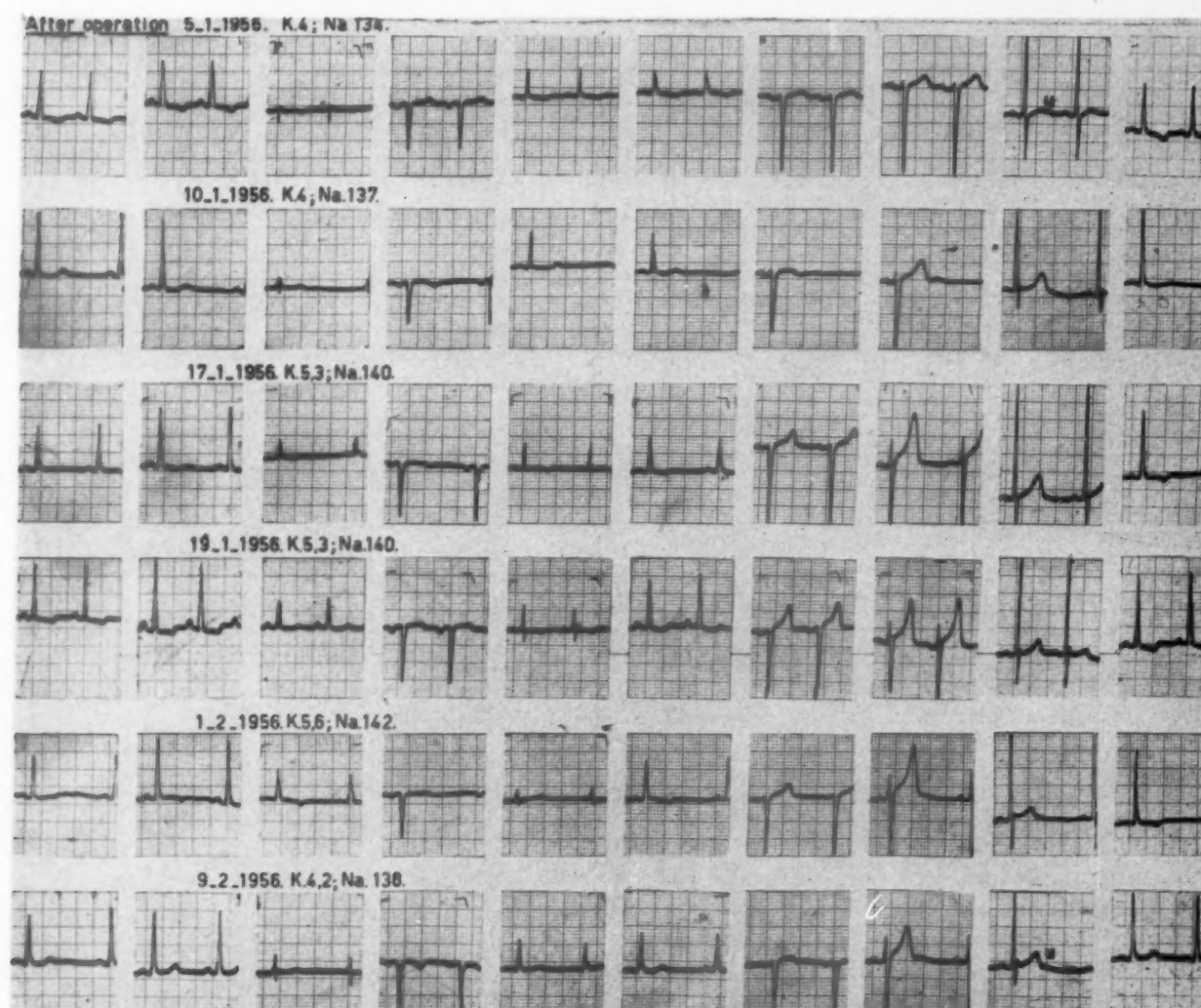


FIG. 2. Primary aldosteronism; postoperative electrocardiogram with serum potassium and serum sodium levels.

Since the findings were rather suggestive of an adrenal tumour, presacral insufflation of air was performed. This clearly outlined the contour of the kidneys and adrenals, but no tumour was demonstrable. Exploratory laparotomy also failed to reveal a tumour but both adrenals showed hyperplasia. The whole right adrenal and about $\frac{2}{3}$ of the left adrenal were resected. The weight of the right adrenal was 7.9 gm., that of the resected part of the left adrenal 8 gm. Microscopic examination (by Dr. A. Arends) proved the cortex of both adrenals to be markedly hyperplastic (the zona fasciculata + zona glomerulosa). Postoperative recovery was uneventful. The blood pressure became normal (130–140/90 mm. Hg); the polyuria and polydipsia disappeared; the serum potassium became 4.5–5 and the serum sodium 132 to 137 mEq./L. The urine excretion was 1,400 to 1,700 ml./twenty-four hours, maximum specific gravity after three weeks was 1.022, and the aldosterone excretion was 10 μ g./twenty-four hours.

The preoperative electrocardiogram showed the

abnormality characteristic of potassium deficiency. (Fig. 1.) At first sight the electrocardiogram seemed to show a left-strain pattern but the simultaneous lowering of the T wave and the rise of the U waves with an apparently prolonged QT indicated the presence of hypopotassemia. The disappearance of the apparent left-strain pattern within a few weeks postoperatively confirmed this explanation. It was also observed that, in agreement with the findings of Lepschkin and Surawicz [3], the QT interval was only apparently prolonged due to the fusion of the T and U waves. The point of transition between T and U could be demonstrated at various places, and it was always found to be precisely iso-electric. After the subtotal adrenalectomy the serum potassium and sodium levels reached normal values in several days, and the aldosterone and potassium excretion decreased as did the sodium retention. It took five weeks, however, before the electrocardiogram became entirely normal again; (Fig. 2.) One week after surgery the T waves were still flat, especially in II,

TABLE I
PRIMARY ALDOSTERONISM

Before operation		Bloodsugar (50gr. gluc) operation		After operation				Bloodsugar 15/3
		3/1	30/1	31/1	9/2	1/3	15/3	
Serum								
K.	1.7-2.5	111	98	6.4	4.2	4.2	4.25	100
Na.	143	150	140	135.2	138	140.5	140	129
Cl.	100	160		108	114	108	108	120
pH	7.44-7.50	154	139	7.29	7.33	7.34	7.39	103
Alk. res.	56 %	154	141	38.1vol%	26vol. %	36vol. %	45.8vol. %	110
Urea	25.2 mg %	120	122	45 mg %	45 mg %	35 mg %	42 mg %	113
Urine								
pH	6.9-7.1		4.6	4.92		5.13	5.3	
titr. acid.				24		29	28	
E.C.G.	hypop. patt.			hypop. patt.	normal	normal	normal	
Bloodpressure	195/125 220/150		140/90	150/100	140/90	150/90	150/95	

AVL, AVF and V6. In the subsequent weeks flat T waves were again observed in I, AVL, AVF and a negative T in V6; the T waves became temporarily negative again in I, II and AVL. Only in V4 did the T wave remain normal after the first week.

This delayed recovery of the electrocardiogram after potassium repletion, with a normal serum potassium level, had been observed previously, although less strikingly, by Schwarz and co-workers [4] in patients recovering from potassium deficiency caused by severe diarrhoea. Weller and co-workers [5] also found, in their experiments with dogs, that the recovery of the ST segment was delayed in comparison with the restoration of the serum potassium level. In agreement with Currens et al. [6], Weller et al. [5] and Huth and Squires [7], we believe that the discrepancy between serum potassium level and electrocardiographic findings should be attributed to the fact that the intracellular rather than the extracellular potassium is of primary significance in the etiology of the electrocardiographic changes.

We were able to find several indications in our patient that recovery of the intracellular equilibrium occurred much later than the extracellular restitution. This was first shown by study of the acid-base balance. Before surgery the alkali reserve and pH were on the high normal side, and "alkaline" urine was consistently excreted (pH 6.9 to 7.1). Postoperatively the urine became markedly acid (pH 4.6 to 4.9), while the alkali reserve fell to 26 volumes per

cent during the course of the first weeks, and the blood pH changed from 7.44 to 7.29. (Table I.) Acidosis during the period of convalescence was also found by Cooke et al. [8,9] in an experimental investigation on rats. After the production of potassium depletion they administered potassium chloride. Subsequently the urine of the rats became very acid (low pH, high value of titratable acidity). These authors explained this phenomenon by the fact that during the period of potassium deficiency the intracellular lack of potassium was partially compensated for by hydrogen ions. In the phase of recovery from the potassium deficiency the hydrogen ions from the cells were again exchanged for potassium ions; this gave rise to an increased acid excretion. It is possible that this mechanism was operative in our patient in whom increased aldosterone production had likewise induced potassium depletion. The electrocardiogram reverted to normal somewhat earlier than the acid-base balance.

An investigation of the carbohydrate metabolism also indicated the retarded intracellular recovery. Preoperatively the blood sugar curve after loading with 50 gm. glucose did not rise very high (about 160 mg. per cent) but the fall proved to be delayed: the initial value was not reached after two hours and thirty minutes. (Fig. 3.) As we have discussed elsewhere *in extenso* [10] this should probably be attributed to an intracellular disturbance of carbohydrate metabolism. During the first four postoperative

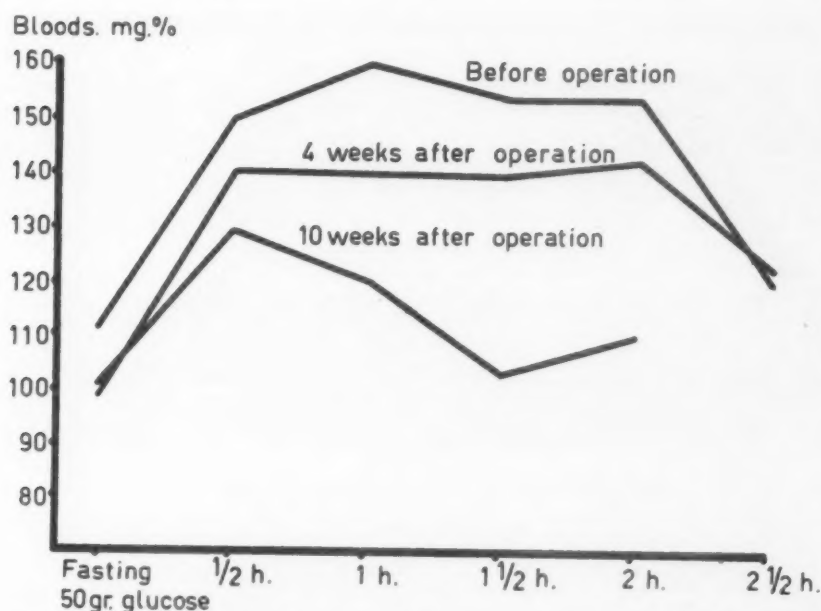


FIG. 3. Primary aldosteronism; blood sugar curves pre- and postoperatively.

weeks we found the same abnormal curve as before the operation; in fact, the glucose tolerance test did not become normal until ten weeks after the operation. (Fig. 3.)

A striking feature was that with such a low serum potassium level our patient never had any pareses or paralyzes before operation. The only abnormality noted was increased fatigability on tetanic stimulation of the muscles. This muscular excitability also recovered slowly postoperatively over a period lasting several months. Nevertheless, a muscle biopsy (carried out during the operation before the patient had been given cortisone) showed a low potassium and high sodium concentration in the muscle: potassium, 67.5 mEq./kg. fresh muscle (normally 91 to 107 mEq.) Na 52.4 mEq. (normally 26 to 36 mEq.). These observations therefore indicate that in potassium deficiency there is no correlation whatsoever between the muscle paralyzes and the electrocardiographic deviations.

In addition to the electrocardiographic changes, microscopic lesions of the myocardium due to potassium depletion have repeatedly been observed in man [11-15], in rats [16,17] and in pigs [18]. It is remarkable that Follis [17] did not observe morphologic changes in the muscles whereas the myocardium showed necrosis and scar formation: "The striated myofibrils as well as the involuntary fibres were not damaged." Our patient, who probably has suffered for many years from a severe potassium deficiency, with significant electrocardiographic abnormalities, did not show morphologic changes in the mus-

cles either (Vos). The available data therefore suggest that the myocardium and the skeletal muscles react in a different way to potassium depletion.

The Electrocardiogram in Familial Periodic Paralysis. The electrocardiographic changes in this rather rare disease were first described by Stewart and co-workers [19]. Biemond et al. [20] were the first to observe a decreased serum potassium level in these patients during paralytic attacks; this was confirmed by many investigators [21-25, and others].

The clinical data of a case observed by us may be summarized as follows:

The nineteen year old patient suffered his first attack of paralysis five years before, during a football game. A fortnight later he had another attack, while he was sitting quietly. The attacks started in the toes and fingers, later spreading to his feet and legs. He was unable to move them, and lost his balance. Later on his neck and arms also became involved. All this passed off when he was able to sleep. Sometimes he woke up during the night unable to move. At times he suffered an attack nearly every day. The duration of the attacks varied from twenty hours to three days. The attacks subsided under treatment with potassium chloride. After an attack, strength first returned to his legs and then gradually to the upper part of his body. There were no warning symptoms preceding the attacks. They generally occurred in the evening or during the night. The attacks were promoted by meals rich in carbohydrates. His appetite was good, micturition and bowel movements were normal. There was no nycturia and no emaciation. His grandfather apparently suffered from the same affection.

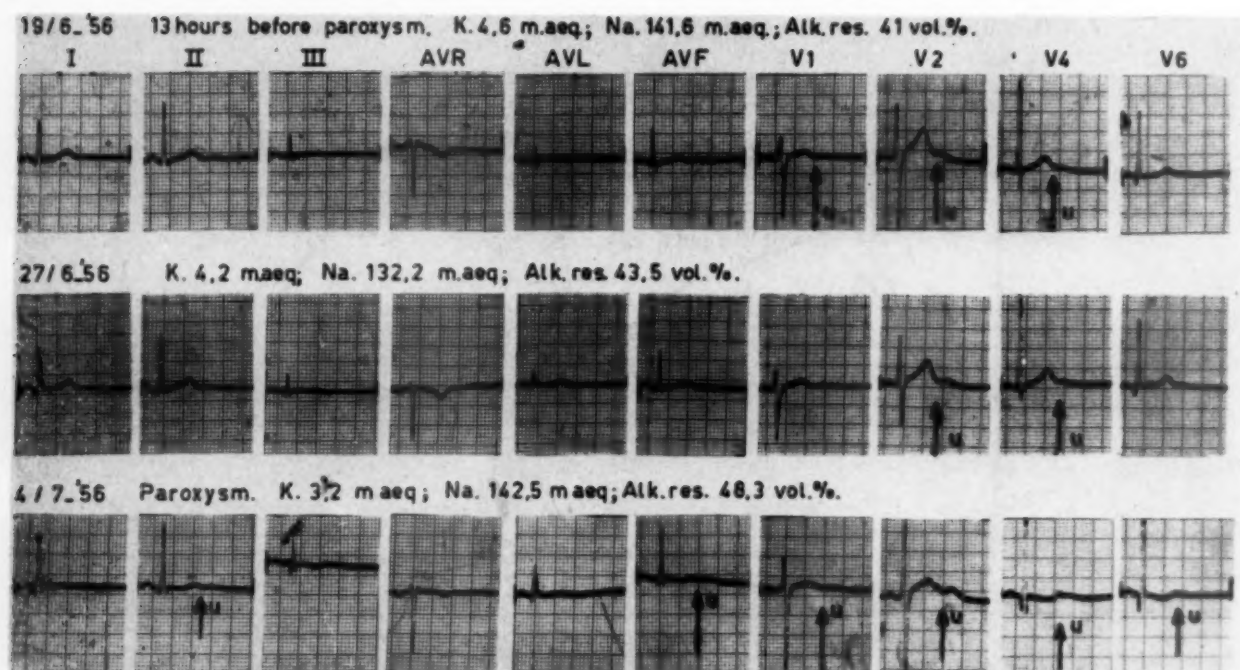


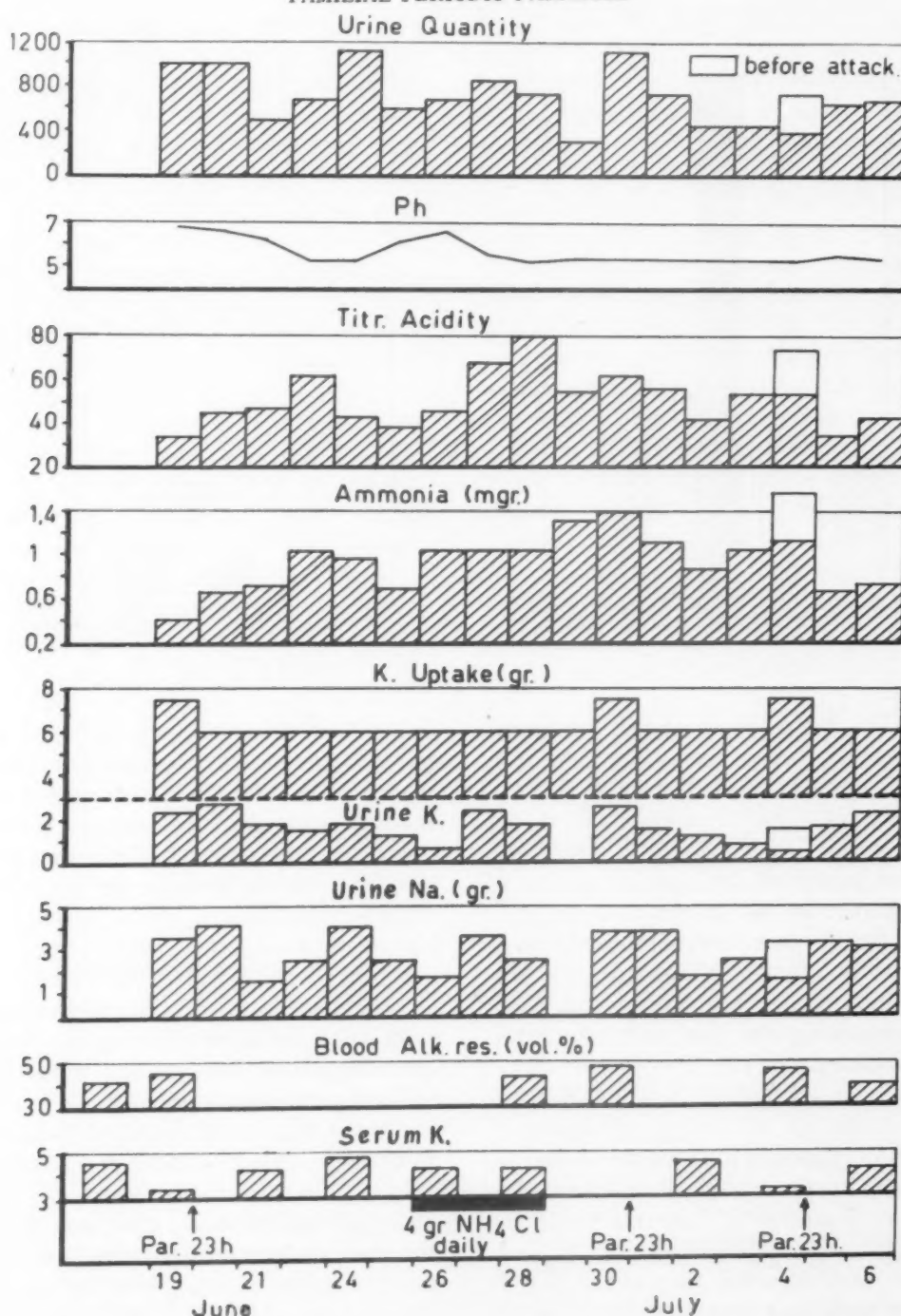
FIG. 4. Familial periodic paralysis; electrocardiograms between attacks and during an attack.

Physical examination did not reveal any abnormalities. The patient was a young man of normal body build. The blood pressure was 125/60 mm. Hg. The heart and lungs were normal. The liver and spleen were not palpable. Apart from the attacks there were no neurologic abnormalities. There were no sensory disturbances during attacks and the state of consciousness was normal. There were no respiratory difficulties.

Examination of the urine showed specific gravity 1.027, no protein, no glucose. The blood hemoglobin level was 97 per cent; erythrocytes 4,910,000, leukocytes 6,400 per cu. mm. The urea clearance was 88.4 per cent, phenolsulfonphthalein 68 per cent. During the attacks the serum potassium level fell to 3.2 mEq./L. When there was no paralytic attack the serum electrolytes were normal (serum potassium, 4; serum sodium, 141 mEq./L.); alkali reserve, 54.4 volumes per cent; pH 7.40. Table II shows the potassium and sodium excretion and also the pH, the acidity of the urine and the ammonia excretion. During this period the patient was given a standard diet. He was given ammonium chloride for a period, and on the day of an attack 1.5 gm. potassium chloride extra. We are indebted to Dr. A. Wettstein for the determination of the aldosterone excretion. This was normal (2.8 to 4 μ g./twenty-four hours), both on the day of an attack and on another day. The excretion of 17-hydroxycorticoids (1.8 mg./twenty-four hours) and 17-ketosteroids (3.8 mg./twenty-four hours) and also of all fractions of the 17-ketosteroids (Table III) was definitely decreased. Between attacks the electrocardiogram was normal. During the paralytic attacks the electrocardiogram showed the abnormality characteristic of hypokotassemia. (Fig. 4.)

The striking difference between this patient and the first one is that the second patient always showed an association of the lowered serum potassium level and the electrocardiographic abnormalities with the paralyzes.

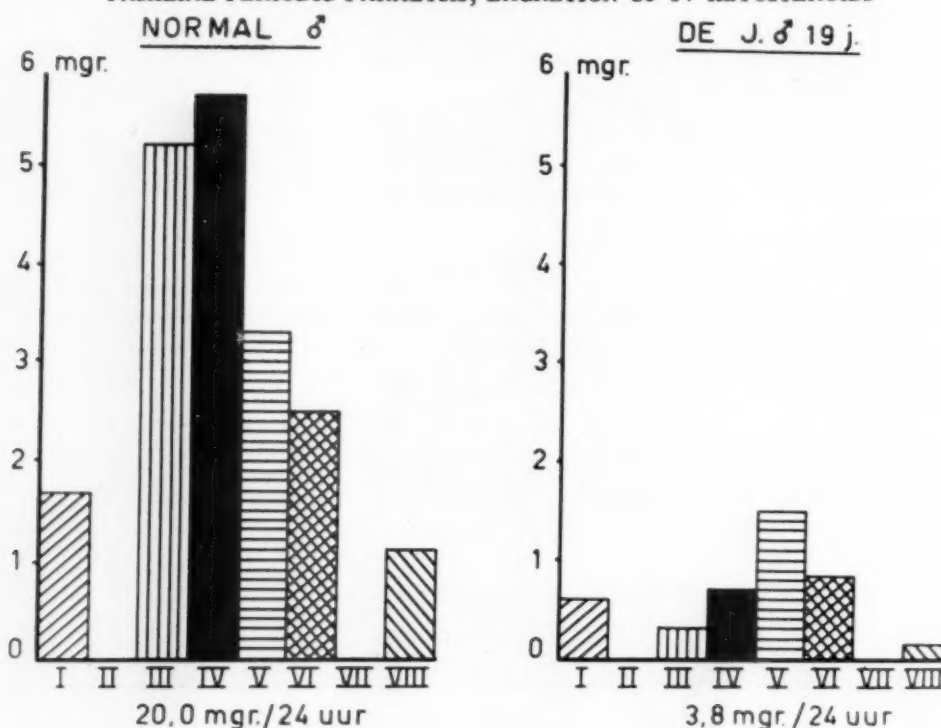
The nature of the change in potassium metabolism in this disease is not yet clear. It is true that the serum potassium level is lowered during the paralytic attacks, even though this fall is not necessarily striking. In some patients the attacks occur at lower potassium levels than in other patients. Occasionally attacks have been observed with normal serum potassium levels [26]. In our patient the serum potassium level was never lower than 3.2 mEq./L. during the attacks. Normal persons generally do not suffer from paralyzes after such a moderate decrease in serum potassium. This suggests that it is not the serum potassium level *per se* which is responsible for the occurrence of the attacks. As Allott and McArdle [27,28] indicated as early as 1938, "... an abnormality of the neuromuscular apparatus being another essential part." Balance studies proved that this fall in the serum potassium level was not caused by an increased potassium excretion; on the contrary, Allot and McArdle [27,28] found a lower excretion on the days of the attacks. Even in our patient, who received an additional 1.5 gm. potassium during the attack, the excretion was not increased. (Table II.) During the attacks Jantz [24] observed a higher potassium concentration in the muscles

TABLE II
FAMILIAL PERIODIC PARALYSIS

than in the absence of attacks. Danowski and co-workers [29] established the occurrence of a shift of potassium from the extracellular into the intracellular space at the onset of the attacks. It is, however, not known to which tissues this shift is directed. On the basis of Jantz's data it seems probable that potassium moves into the muscle cell. Zierler [30] demonstrated the occurrence of a nocturnal shift of potassium into the muscle cell, which was five to ten times greater in

patients with periodic paralysis than in normal persons. The observed rate of entry into muscle of up to 1 mEq. potassium/hour/kg. muscle might well account for the concurrent disappearance of potassium from the extracellular fluid. Initially there seems to be an increased potassium requirement of the muscles; these demands are satisfied from extracellular sources of potassium, and thus the fall in the serum potassium level is brought about. The cause of

TABLE III
FAMILIAL PERIODIC PARALYSIS; EXCRETION OF 17 KETOSTEROIDS



this temporarily increased potassium requirement is unknown. It has been suggested that there is a deficiency of ionized potassium [24], possibly due to binding of potassium to the muscular proteins [37]. In these patients the attacks can be produced by administration of large doses of glucose, by injection of insulin, and especially by the combined administration of glucose and insulin. By these measures the shift of potassium into the cells is stimulated, since potassium is necessary for intracellular carbohydrate metabolism.

The muscle paralysis usually disappears when potassium chloride or citrate is administered and the paralytic episodes may be prevented by prescribing a high protein low carbohydrate diet, with moderate quantities of fat; this keeps the serum potassium level normal [32].

Conn et al. [33] reported that the paralytic attack in these patients is preceded by retention of sodium and that recovery from the attack was associated with massive sodium diuresis. They consider sodium retention to be the primary factor which sets into motion the characteristic chain of events in an episode of periodic paralysis, but they add that this does not mean that a sudden increase of intracellular potassium does not influence the onset of a paralytic attack. The observation in our patient with primary aldosteronism of a marked increase in the sodium content of the muscle without paralysis indicates that sodium retention in the muscle cell in itself is not the essential abnormality. As Conn also has suggested, the sum of the intracellular cations may be a critical factor in the muscular paralysis (*cf.* Cannon [34]).

CONCLUDING REMARKS

As indicated in the discussion of the first patient, the electrocardiographic abnormalities occur regularly as a result of intracellular potassium depletion even when the extracellular level is normal. In periodic paralysis, potassium depletion may develop in the myocardium as a result of the shift of potassium towards the cells of the skeletal muscles; this probably also causes the fall in the serum potassium level. These considerations explain the close parallel between the decrease of the serum potassium level and the electrocardiographic changes in periodic paralysis. Our data suggest a remarkable difference between the myocardium and the skeletal muscles in their responses to potassium depletion. In our first patient with aldosteronism muscle paresis developed only during the first few post-operative days. It is fairly certain that in this phase there was a shift of potassium into the muscle cells. In other conditions muscle paraly-

due to potassium depletion also occur particularly during the phase of a shift of potassium into the cells (paralysis in the treatment of diabetic coma with large amounts of glucose and insulin). In this connection one should remember that paralyzes similar to those seen in hypopotassemia have been observed in patients with increased plasma potassium due to severe renal insufficiency [35,36]. It is difficult to obtain adequate data on the ratio of intracellular and extracellular potassium levels in these complicated conditions.

It would appear from the available data that the conditions leading to the development of muscular paralysis are different from those responsible for the occurrence of the electrocardiographic changes. A sudden marked shift of potassium into the cells seems to be especially important. The chances for this are greater when an intracellular potassium deficiency exists. Severely disturbed muscular reactions to tetanic stimulation, however, have not been found when potassium depletion was produced gradually in experimental animals [37]. Under these circumstances sudden shifts of potassium into the cells are less likely to occur.

The observation that in our patient with primary aldosteronism paralyzes did not develop while in other reported cases it did, may possibly be related to the fact that our patient was the only case of primary aldosteronism due to adrenal hyperplasia. Perhaps he had a more steady production of aldosterone. In the cases of Conn [33], Chalmers [39], Foye [40] and others, an adenoma or a carcinoma of the adrenal cortex was found. In analogy with the adenoma of the islets of Langerhans it is possible that the secretion may vary from day to day in the case of tumours. These variations may result in changes in the intracellular ionic milieu which cause periodic paralyzes. In our patient, also, the urinary aldosterone excretion was higher than in the patients with adenomas.

SUMMARY

A patient with primary aldosteronism due to hyperplasia of the adrenal cortex showed the electrocardiographic abnormalities characteristic of hypopotassemia. Some days after subtotal adrenalectomy the serum potassium level became normal, but the electrocardiogram did not return to normal until five weeks after the operation. This is attributed to a delayed recovery of the intracellular electrolyte relation-

ships; this hypothesis is supported by the observation that the acid-base balance and carbohydrate metabolism did not revert wholly to normal until several weeks after the operation. When the serum potassium level was very low, paralyzes did not occur. They were observed, however, several days postoperatively when the serum potassium level had already returned to normal and a shift of potassium from the extracellular to the intracellular space might be assumed.

Different mechanisms are responsible for the development of the paralyzes and of the electrocardiographic abnormalities. There is a striking difference between the reaction of cardiac and of striated muscle to potassium deficiency.

In familial periodic paralysis, in contrast, the paralyzes and the electrocardiographic changes take a parallel course. Here the paralyzes are probably correlated with a shift of the potassium from the extracellular space into the striated muscles, which may possibly explain why potassium is withdrawn from the myocardium.

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Adynamia Episodica Hereditaria*

A Disease Clinically Resembling Familial Periodic Paralysis but Characterized by Increasing Serum Potassium during the Paralytic Attacks

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NEUROLOGIC symptoms are observed in the presence of increased as well as of decreased serum potassium. In both conditions paralysis occurs; in hyperpotassemia there are also paresthesias. Hypopotassemia can be caused by the following factors singly or in combination: increased loss of potassium in the urine or faeces, insufficient potassium intake (increase in the extracellular fluid volume of potassium-free fluids) and by increased intracellular accumulation of potassium [1]. A shift of potassium from the extracellular to the intracellular spaces is assumed to occur in familial periodic paralysis, a disease characterized mainly by flaccid paralysis accompanied by decreased serum potassium [2]. Investigation of the potassium balance in this disorder has shown that there is no increase in urinary potassium loss during the attacks and therefore the hypopotassemia is ascribed to potassium entering the cells [3-7].

Hyperpotassemia can occur in the presence of decreased excretion of potassium in the urine because of impaired renal or adrenocortical function [8,9] and in widespread cellular destruction [1,10]. Experimental production of hyperpotassemia with neurologic signs in a normal subject requires an oral dose of 5 to 15 gm. of potassium (as a salt). Paresthesias are not uncommon, but even this large dose produces muscle weakness only in exceptional cases [11-13].

This paper is concerned with a review of a familial disease characterized mainly (like familial periodic paralysis) by attacks of paralysis of

the extremities and the muscles of the trunk. Unlike familial periodic paralysis, however, the serum potassium increases during the attacks, without administration of potassium salts and without any demonstrable decrease in the excretion of potassium in the urine. Even so small an oral dose as 1 to 2.5 gm. of potassium may cause paralysis and increase the serum potassium. The disease had been called adynamia episodica hereditaria. (Readers interested in details are referred to earlier publications [14-17].)

MATERIAL

In a Swedish-Danish investigation two families were found with hereditary episodic adynamia. Both families were traced back to the south of Sweden, from where one branch of one of the families had moved to Denmark some fifty years ago. Of this family, which can be dated back to the year 1700, a total of 122 affected members are known. The other family had been described in 1902 by Kulneff [18], who called the disease myatonia periodica. Now, after further investigation, sixteen members of this family are known to have been affected.

Of the 138 patients, ages ranging from four to ninety-two years, seventy-three were males and sixty-five females. Eighty-seven were examined personally by the authors. Data on the remainder were obtained from Kulneff's paper, by correspondence with the patients or by information from their close relatives. Seventeen of the patients were admitted to the University Hospital, Lund, for observation (I. G.) and three to the Finsen Institute in Copenhagen (U. S.). Details of the methods of study are given elsewhere [15,19].

* From the Pediatric Clinic, University of Lund, Sweden; the University Institute for Human Genetics, Copenhagen, Denmark; the Royal Medical Board, Stockholm, Sweden; the Finsen Institute and Radium Center, Central Laboratory, Copenhagen, Denmark.

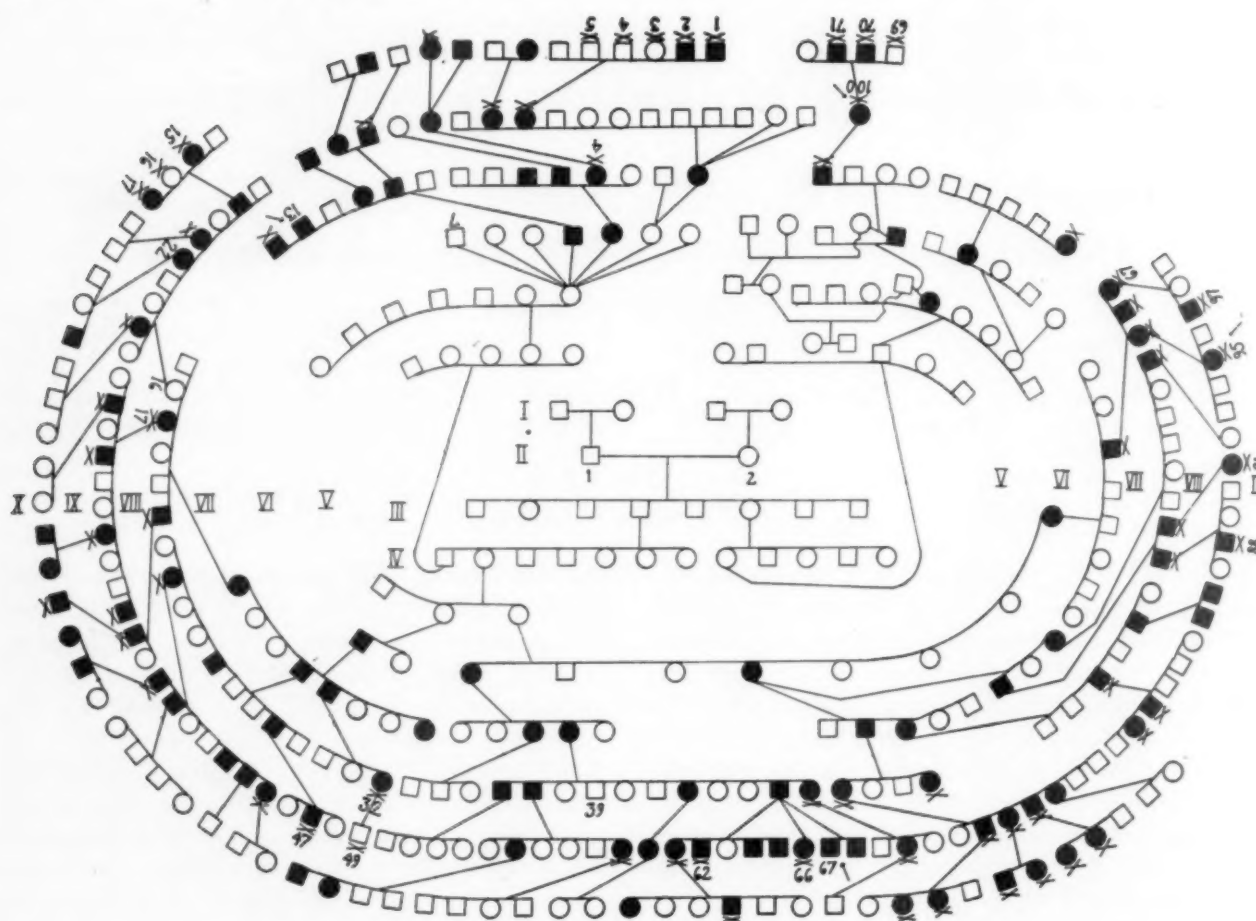


FIG. 1. Family 1. ■ affected male, ● affected female, □ male, unaffected or state of health unknown, ○ female, unaffected or state of health unknown, ↗ proband, X examined personally.

RESULTS

Etiology. The disease is hereditary. The inheritance is due to a single autosomal dominant gene with complete or almost complete penetrance. (Figs. 1 and 2.)

Pathology. The patients who have been examined postmortem died of some intercurrent disease. No search had been made for changes referable to adynamia.

Muscle tissue was taken from five patients for histologic examination.* In one patient (sixty years old), who had had the disease since the age of one, a biopsy specimen from the anterior tibial muscle showed changes of the type seen in dystrophia myotonica [20]. This patient, however, differed clinically from the remainder in that he also had slight muscle atrophy and weakness of the extremities between attacks.

*The examinations were performed by Professor G. Wohlfart (Lund) and Dr. Erna Christensen (Copenhagen).

Histologic examination showed no changes in the other four patients.

Symptoms. The age at onset of the disease in 108 patients was known. In forty-eight the onset occurred before the age of five, and in ninety-nine before the age of ten. The youngest age at onset was eight months, the oldest thirty-one years.

The attacks are precipitated by rest after physical exertion. The more intense the exertion, the more severe the attack. The attacks occur only after the patient has rested for some minutes to a few hours, usually about an hour—a limb is never paralysed during exercise. The attacks are more severe and more frequent in damp cold weather. Hunger has a similar effect, while the intake of food, especially bread, has a certain prophylactic and therapeutic effect.

The attack begins with a feeling of heaviness of the limbs accompanied by acroparesthesias. These symptoms are followed by muscle weakness usually beginning in the legs and sometimes

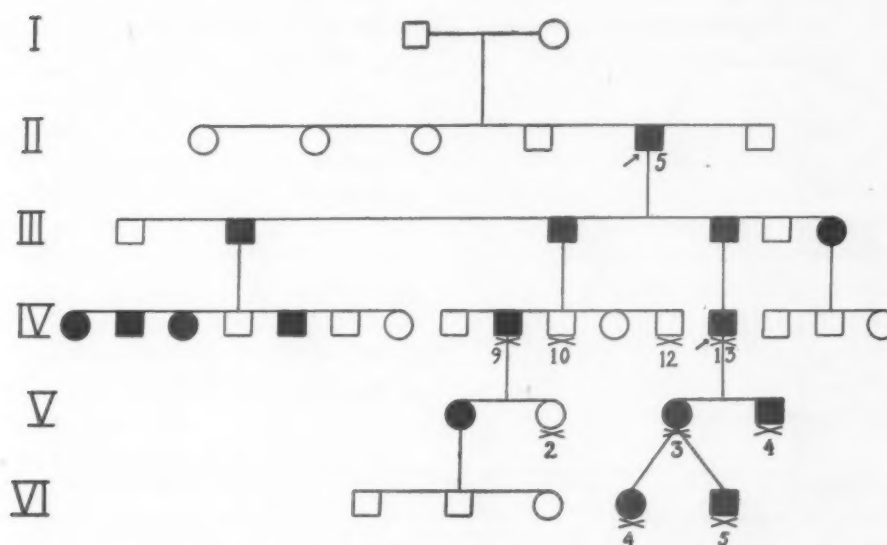


FIG. 2. Family 2. ■ affected male, ● affected female, □ male, unaffected or state of health unknown, ○ female, unaffected or state of health unknown, ↗ proband, X examined personally.

in the arms. The attacks vary in extent and severity although complete paralysis is rare. Usually the patient can turn on the examination table or bed and sit up, but he cannot stand or walk. Occasionally, mild respiratory trouble occurs. About half the patients have had facial paralysis and/or articulation difficulties at some time or other. The attacks are more common during the day than at night.

The attacks occur at irregular intervals. The frequency may vary from several attacks a day to once a year. About three-fourths of the patients had an average of one attack a week. The duration varied from a few minutes to a day, although it was usually thirty minutes to one hour. Gentle exercise can ward off or shorten an attack.

During childhood the attacks are, as a rule, short and frequent. At puberty they become longer and more severe. After thirty years of age about half the patients experience improvement, the attacks then being less severe and less frequent. Sometimes the attacks cease after the age of fifty to sixty.

As a rule, the patients feel well between attacks. About one-third, however, state that, especially during the cold season, the attacks are followed by dull pain, tenderness and stiffness, symptoms which may persist for days or weeks.

Signs. During a free interval, neurologic examination, as a rule, reveals nothing abnormal. In two patients slight weakness of the muscle of the limbs was noted between at-

tacks; one of these also had muscle atrophy, the only one in the entire study. During hospital observation clinical and laboratory studies between attacks showed no signs of endocrine disorders, renal injury or abnormal levels of serum electrolytes (K, Na, Ca, Mg, P, Cl). The cerebrospinal fluid was also found to be normal (two patients studied). The total exchangeable potassium was within normal limits [19] (three patients studied). Ophthalmologic examination showed no cataract or malformation. The sensitivity of the patients to intravenous administration of d-tubocurarine (four patients studied) and succinylcholine (five patients studied) also was within normal limits [21,22]. The patients were examined during a total of eighty-one attacks (sixty-one attacks in seventeen patients in Lund and twenty attacks in three patients in Copenhagen). The attacks were precipitated either by rest after physical exertion (thirty-eight attacks) or by oral administration of 1 to 7 gm. of potassium. The clinical picture did not vary with the method of precipitation. The paralysis started within ninety minutes of the end of physical exertion or of the administration of potassium and culminated a few minutes to one hour later. The duration of the attack varied from twenty minutes to more than one day. All degrees of severity were noted, but respiratory distress was never observed.

In over half the attacks the autoreflexes were weakened or absent. In a somewhat smaller number Chvostek's sign became positive. Pupils

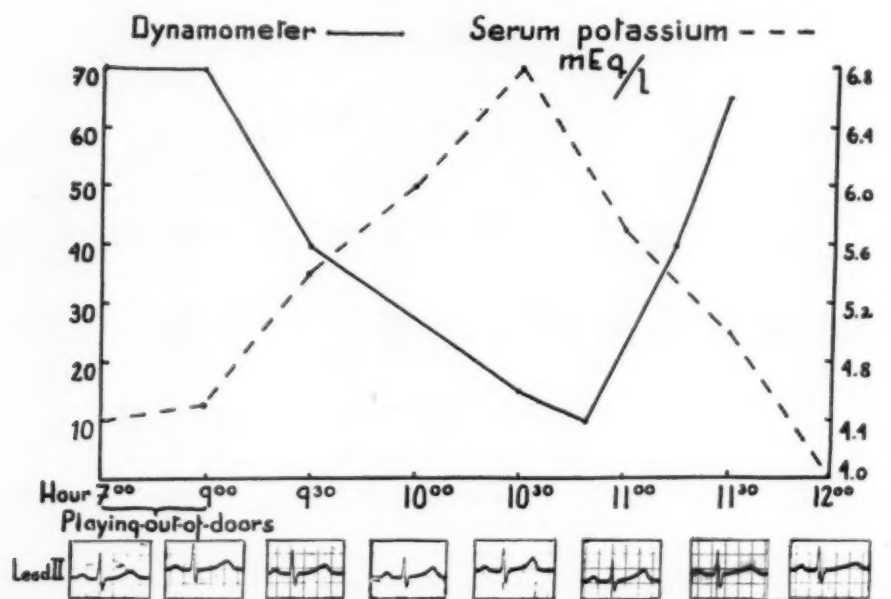


FIG. 3. Changes in serum potassium and electrocardiogram during a typical attack, precipitated by exercise, in a boy aged ten.

lary and plantar reflexes were normal, as was excitability upon electric stimulation. No sensory disturbances other than initial paresthesias were noted. The muscles were not tender, they were of normal tone, and showed no signs of myotonia. There was no change in the level of consciousness.

The serum potassium was determined before precipitation of the attack and then at intervals of at most half an hour until paralysis appeared and disappeared. In forty-five of forty-nine attacks studied the serum potassium increased to a maximum which coincided within \pm fifteen minutes of the culmination of the attack (twenty-three attacks precipitated by administration of potassium). In one case it was unchanged and in three it decreased. (In these four attacks potassium was not administered.) The increase varied between 0.2 and 3.2 mEq./L. Only in half the attacks precipitated by rest after exertion did the maximal serum potassium value exceed the upper limit of normal (5.5 mEq./L.) [23]. In most of the attacks precipitated by administration of potassium salts, however, this limit was exceeded.

Electrocardiographic changes, namely higher and sharper T waves, accompanied the increase in serum potassium; these disappeared as soon as the serum potassium level had again become normal. The changes in serum potassium and in the electrocardiogram during a typical attack precipitated by rest after exercise are illustrated in Figure 3.

The excretion of potassium in the urine was, as a rule, higher during the attack than during a free interval.

In 75 per cent of the attacks the number of circulating eosinophils decreased by at least 50 per cent of the original value. The serum phosphorus decreased slightly in six of eight attacks. The other blood components examined [hematocrit, blood sugar, serum sodium, serum calcium, serum magnesium (two patients studied), serum chloride] showed no changes. The urine was of normal colour and contained no hemoglobin or urobilinogen.

In two patients studied the electroencephalograms before and during attacks were of the same normal appearance. Six patients were examined electromyographically.* During attacks the innervation pattern on maximum effort changed, suggesting loss of active muscle fibers. The mean duration of the action potentials decreased significantly in comparison with that noted between attacks. Furthermore, spontaneous activity increased during attacks.

The threshold of motor response to intra-arterially injected acetylcholine† was low both during and between attacks in five patients studied [24].

As many of the patients and their relatives as

* The examinations were carried out at the Neurophysiological Institute, Copenhagen, and the curves were interpreted by Professor F. Buchthal.

† The examinations were performed by Dr. Lise Engbaek, Copenhagen.

possible were classified according to blood groups. The distribution among the various groups was found to be the same for affected and unaffected subjects. On the other hand, a correlation was found between the gene for adynamia and the Duffy system. This connection might be due to genetic linkage and is the subject of current closer analysis.

Diagnosis. Sometimes inquiry into the history is sufficient to make the diagnosis. Knowledge that the disease occurs nearly always in one of the parents of the patient and his family is useful. However, verification of the diagnosis requires examination during an attack.

The attack can be precipitated by rest after exertion or by oral administration of potassium salts. In both cases the patient should be in the fasting state. A dose of 4 gm. of potassium chloride for adults, 3 gm. for older children and 2 gm. for young children is usually sufficient. If, however, this does not precipitate an attack the dose may be increased by 1 gm. in a subsequent test. In the present investigation these doses were found to be sufficient and not dangerous. It should be stressed, however, that potassium salts should not be given to patients with decreased adrenocortical or renal function.

The serum potassium should be determined and/or electrocardiograms taken on at least three occasions; before the attack, at the culmination of the attack, and after the attack. A transient increase in the serum potassium level and/or electrocardiographic changes of the type seen in hyperpotassemia during an attack establishes the diagnosis. A single examination might, however, give results within the normal variation and therefore may not be of diagnostic value.

Differential Diagnosis. Adynamia episodica hereditaria has hitherto not been clearly distinguished from familial periodic paralysis; some of the cases published under the latter diagnosis are probably examples of episodic adynamia [25-27]. Inquiry into the familial history can provide the key to the differential diagnosis. Determination of the serum potassium and electrocardiographic examination as well as the patient's reaction to potassium decide the diagnosis. In the inherited form of myoglobinuria [28] pain and muscle tenderness are more marked than the manifestations of paralysis. In such attacks the urine is red and gives a positive benzidine reaction. In attacks of porphyria the paralysis is accompanied by deterioration of

the general condition, abdominal pain, vomiting and constipation. The urine gives a positive urobilinogen reaction. Inquiry into the history is sufficient to exclude confusion with other neuromuscular diseases. A spontaneous increase in the serum potassium in an individual without signs of adrenocortical or renal disease is specific of adynamia episodica hereditaria, as is the paralytic response of such a person to administration of so small a dose of potassium as 1 to 2.5 gm.

Course and Prognosis. After thirty years of age the disease usually regresses. It has as yet never led to complete disability; neither has it ever been fatal.

Therapy. The patients state that gentle exercise or the intake of food will often shorten the duration of symptoms. The disease is less troublesome if the patients follow a regimen consisting of moderate physical exertion, sufficient sleep and regular meals at fairly short intervals. Various methods were tried to prevent or ward off an attack in those patients admitted for observation. Intravenous injection of calcium gluconate at the culmination of an attack curtailed the symptoms in fourteen of fifteen attacks.

The administration of glucose (100 to 150 gm. orally) alone or together with insulin (20 I.U. subcutaneously) during the attack had no demonstrable effect. When administered about half an hour before an otherwise provocative dose of potassium the latter produced at most only slight symptoms.

SUMMARY

A disease designated adynamia episodica hereditaria is described. The disease is inherited as a monohybrid, autosomal dominant with complete or almost complete penetrance.

The disorder usually makes its first appearance in childhood. It is characterized by intermittent attacks of paralysis with symptom-free intervals.

During the attacks the serum potassium level increases, without any decrease in urinary potassium. Attacks can be provoked by oral administration of 1 to 2.5 gm. of potassium. Electrocardiographic and electromyographic changes are demonstrable during attacks. The motor response to acetylcholine is increased during and between attacks.

Premedication with glucose inhibits the provocative effect of potassium salts. Calcium

administered intravenously during an attack promptly controls the symptoms.

Adynamia episodica hereditaria is undoubtedly a clinical entity. No other disease is known in which the serum potassium level increases spontaneously without decreased excretion of potassium in the urine, and without signs of widespread cellular destruction, and in which oral administration of 1 to 2.5 gm. of potassium is sufficient to precipitate paralysis, with elevation of the serum potassium. The spontaneous increase in serum potassium is probably due to excessive leakage of potassium from the cells. The beneficial effect of glucose administered before an otherwise provocative dose of potassium argues in the same direction.

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Potassium Deficiency of Renal and Adrenal Origin*

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ABNORMAL urinary loss of potassium is a feature common to certain disorders of both the kidney and the adrenal cortex. That potassium metabolism is under the control of the adrenal cortex has been known since the discovery of a rise in the plasma potassium of adrenalectomised rats [7] and of patients with Addison's disease [2]. Conversely, a fall in plasma potassium, associated with a systemic alkalosis, may be found in Cushing's syndrome [3] and after administration of ACTH, adrenal cortical extracts, desoxycorticosterone and cortisone. Recently potassium deficiency, together with hypertension and alkalosis but without other features of Cushing's syndrome, has been shown to be caused by certain adrenal cortical tumours which produce excessive amounts of aldosterone [4,5].

Loss of potassium may also be due to intrinsic disorders of the kidney. Such disorders have not often been described. In the condition known as renal tubular acidosis, which at least in older children and adults is rare, potassium deficiency is often present. It is probably produced by a congenital defect in tubular function and is sometimes familial, the essential disability appearing to be an inability to produce an acid urine. In consequence acid radicals are excreted in combination with basic ions including potassium. In contrast to the alkalosis and potassium deficiency resulting from over-activity of electrolyte-controlling adrenal cortical hormones, in renal tubular acidosis there is a systemic hyperchloraemic acidosis and the urine is alkaline or only faintly acid.

From time to time cases of potassium deficiency have been reported to result from acquired renal disease—pyelonephritis, chronic nephritis or malignant hypertension.

In this paper the clinical and biochemical features of three patients are described; the

first patient suffered from an adrenal cortical tumour with excessive production of aldosterone; the second from renal tubular acidosis; the third, who clinically and in many biochemical aspects closely resembled the first patient, could not be proved to have the same disorder, and the difficulties of diagnosis are discussed.

METHODS

Chemical analysis and collection of metabolic data were as previously reported [6] with the following exceptions and additions. Renal clearances were conducted as described by Goldring and Chasis [7] and the chemical methods for mannitol and PAH also came from this source. Inulin was determined by the Selivanoff reaction [8]; chloride by the iodometric method of van Slyke and Hiller [9]. 17-keto- and 17-ketogenic steroids were determined by Gibson and Norymberski's method [10]; aldosterone by paper chromatography according to Neher and Wettstein [11] and plasma hydrocortisone by the Bush system [12].

CASE REPORTS

CASE 1. *Adrenal cortical tumour with excessive production of aldosterone:* This man, a police officer, was first seen at the Royal South Hants Hospital in December, 1950, at the age of thirty-five. He had had scarlet fever as a child, and an appendicectomy at age thirty-one. He complained of exertional dyspnoea of eighteen months' duration and of periodic headaches for two years. His blood pressure was 205/120 mm. Hg and early hypertensive retinal changes were present. The patient failed to attend the hospital again until March, 1952, when he complained of some visual disturbance and of dyspnoea on exertion. The blood pressure was again 205/120 mm. Hg and there was an area of oedema at the right macula, considered to be due to vascular occlusion or old haemorrhage. He was treated with hexamethonium bromide for approximately three months but it had no effect on the hyper-

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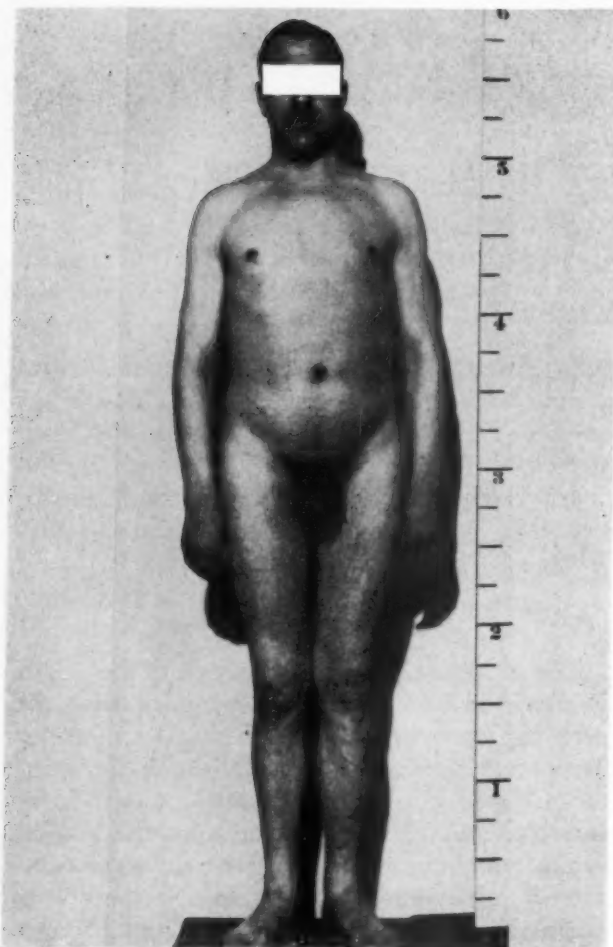


FIG. 1. Case 1. Adrenal cortical tumour, without bodily appearance of Cushing's syndrome.

tension. He was not seen again until January, 1955, when he was admitted to the Royal South Hants Hospital. Now aged forty, the patient complained of more severe dyspnoea on exertion, his exercise tolerance being limited to thirteen stairs taken slowly. Two months previously he had had one severe attack of dyspnoea while sitting in a chair, and thereafter had found it more comfortable to sleep in a propped-up position. His most striking symptom was nocturnal polyuria, which drew our attention to the electrolyte balance and led to the correct diagnosis. For some months he had passed 4 to 6 pints of urine by night and normal quantities by day. There was serious interference with his sleep. For a year he had noticed decreasing libido and some loss of potency; for six months he had noticed some oedema of the ankles. He had lost no weight.

On examination, the patient was a heavily built, heavily featured man (Fig. 1), but he was neither obese nor plethoric. There were no striae. Both ankles were oedematous. The blood pressure was 230/120 mm. Hg. The pulse rate was 72 per minute and occasional extrasystoles were present. The aortic second sound was accentuated and there were no murmurs.

The cardiac impulse was not palpable but radiologic examination showed the left ventricle to be enlarged. The jugular venous pressure was normal. The nervous system, chest and abdomen were normal. The fundi appeared normal on ophthalmoscopic examination but small scotomas were demonstrated in both macular areas.

The following investigations suggested that the patient was suffering from overactivity of the adrenal cortex. The urinary output of 17-ketosteroids was 29, 25 and 53 mg. (normal 5 to 21 mg.) and of 17-ketogenic steroids 46, 55 and 86 mg. (normal 5 to 18 mg.) on three successive days. The plasma electrolytes (in mEq./L.) were: sodium, 138; potassium, 2.5; chloride, 98; and bicarbonate, 40. The nocturnal polyuria was confirmed, the patient passing an average volume of 1,260 ml. during the day and 2,240 ml. during the night. The Kepler test gave the following values: the night urine was 1,670 ml. and hourly volumes thereafter during the morning were 110, 242, 210, 98 and 128 ml. The night urinary chloride concentration was 75 mEq./L. and the urea 910 mg. per cent; the serum chloride was 96 mEq./L., and the serum urea 41 mg. per cent. Kepler's factor A was 4.1.

Estimation of renal function showed the urea clearance to be 87 per cent of average normal with a blood urea of 38 mg. per cent. The urine contained a trace of protein. Radiologically the skull, spine and lungs were normal.

In February, 1955, the patient was transferred to St. Thomas's Hospital where the history and physical findings were confirmed. The patient's temperature was 99°F. in the evenings and continued to be so regularly. In addition a mass was palpated in the left hypochondrium which moved on respiration and felt like the tip of the spleen. The patient's height was 5 feet, 10 inches (178 cm.) and his weight was 179 pounds (81 kg).

Metabolic studies and clinical investigations were carried out for a period of forty-seven days (days 0 to 46) with the following results:

On days 1 and 7 the plasma electrolytes in mEq./L. were: sodium, 142, 142; potassium, 2.7, 2.5; chloride, 98, 92; and bicarbonate, 44 and 42, respectively.

The electroencephalogram (day 1) was dominated by an 8 cycles/second alpha rhythm. Generalised, low voltage 20 cycles/second fast activity was present, and also 3 and 5 cycles/second low voltage slow activity, the latter being evident on hyperventilation. The record was considered to be mildly abnormal without diagnostic features and without focal activity.

The urine had a specific gravity of 1.008 and contained a small amount of protein, but no reducing substances or ketone bodies. The blood urea was 38 mg. per cent, the plasma creatinine, 1.6 mg. per cent. On day 1 the creatinine clearance, estimated on a twenty-four-hour specimen of urine, was 78 ml. per minute. On day 3, after deprivation of fluid for twenty-

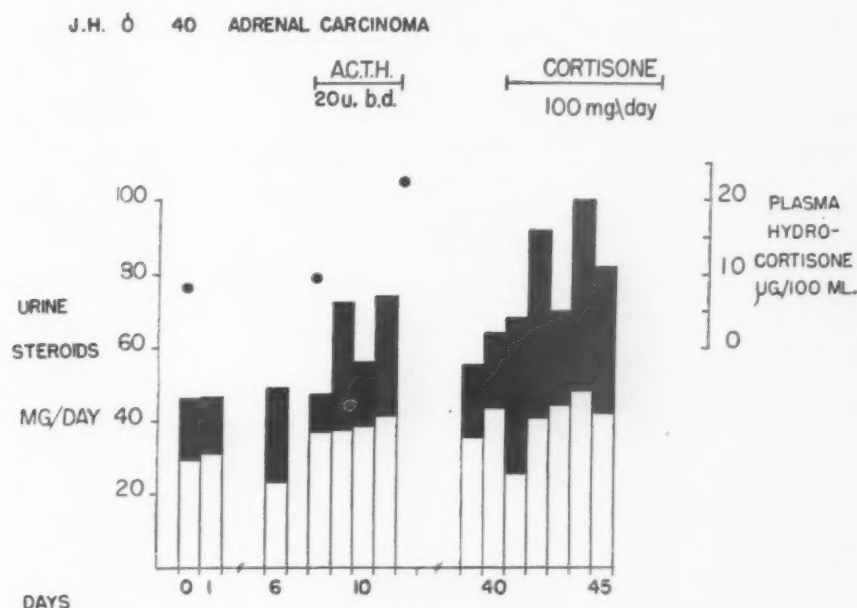


FIG. 2. Case 1. Urinary steroid excretion during the administration of ACTH and cortisone; and plasma hydrocortisone concentration. The white portion of each block represents the output of 17-ketosteroids; the total height to the top of the black portion, the output of 17-ketogenic steroids. Plasma hydrocortisone concentration is shown by the solid black dots.

eight hours, during which 2,670 ml. of urine were passed, the urinary specific gravity was 1.012. The patient then drank 1,200 ml. of water, and passed 50, 45, 35 and 45 ml. of urine within the next four hours, with no change in specific gravity. With a pitressin® infusion of 3 milliunits per minute the urinary osmolarity was 540 mOsm./L., corresponding to a specific gravity of approximately 1.017.

An intravenous pyelogram showed normal excretion of dye, but the left kidney was low in position.

The urinary output of 17-ketosteroid was 29, 31 and 33 mg. and of 17-ketogenic steroids 46, 46 and 49 mg. on days 0, 1 and 6. The plasma hydrocortisone was 8.3 and 10 µg. per 100 ml. on days 0 and 8 (normal 2 to 8 µg. per 100 ml.). The response to ACTH is shown in Figure 2. ACTH gel (Armour N 31605) in a dose of 20 units was injected intramuscularly twice daily for four days (days 8 to 11). On these days the urinary output of 17-ketosteroids was 37, 37, 38 and 41 mg., and of 17-ketogenic steroids, 47, 73, 56 and 74 mg. Eosinophil counts were 38, 9, 0 and 19 cells per cu. mm. The urinary sodium (on an uncontrolled intake) was 53, 122, 109 and 117 mEq./day, compared with previous values of 151, 160 and 87 mEq./day. The plasma hydrocortisone rose to 23 µg. at the end of the fourth day of ACTH administration.

On three days the urinary aldosterone was 20, 20 and 30 µg. per day (normal for the method used, up to 2 µg. per day). Sodium and potassium intake were normal on these days.

The total plasma proteins on day 7 were 7.3 gm. per cent with a normal electrophoretic pattern on filter paper.

The haemoglobin on day 0 was 100 per cent (Haldane). White blood cells numbered 7,400 per cu. mm., of which 82 per cent were polymorphonuclears, 15 per cent leukocytes and 3 per cent monocytes. The erythrocyte sedimentation rate was 11 mm. in one hour (Westergren).

The fasting blood sugar on day 6 was 110 mg. per cent. After 50 gm. of glucose had been administered orally, the blood sugar at half-hourly intervals was 133, 204, 221, 192, 149 and 112 mg. per cent. The urine contained no reducing substances at one hour and a trace at two hours.

The fasting blood sugar on day 7 was 104 mg. per cent. At twenty, thirty, forty-five, sixty and ninety minutes after intravenous injection of 0.1 unit per kg. of body weight of soluble insulin the blood sugar was 71, 62, 71, 87 and 103 mg. per cent respectively.

Presacral air insufflation (day 15) showed a mass approximately 3 inches in diameter above the left kidney. Following this procedure the patient had surgical emphysema of the neck for three days.

A study was made of the effect of changing intake on the sodium and potassium balances; the results are shown in Figure 3.

First period (days 13 to 26): A diet containing 28 mEq. per day of sodium and 159 mEq. per day of potassium was given from day 13 to day 26. From days 19 to 25 faecal sodium was 2 mEq. per day (normal 0.5 to 3 mEq. per day) and faecal potassium 47 mEq. per day (normal 10 to 18 mEq. per day). They were not estimated for days 13 to 18.

On the first two days of this diet (days 13 to 14) there was a small negative balance of sodium, fol-

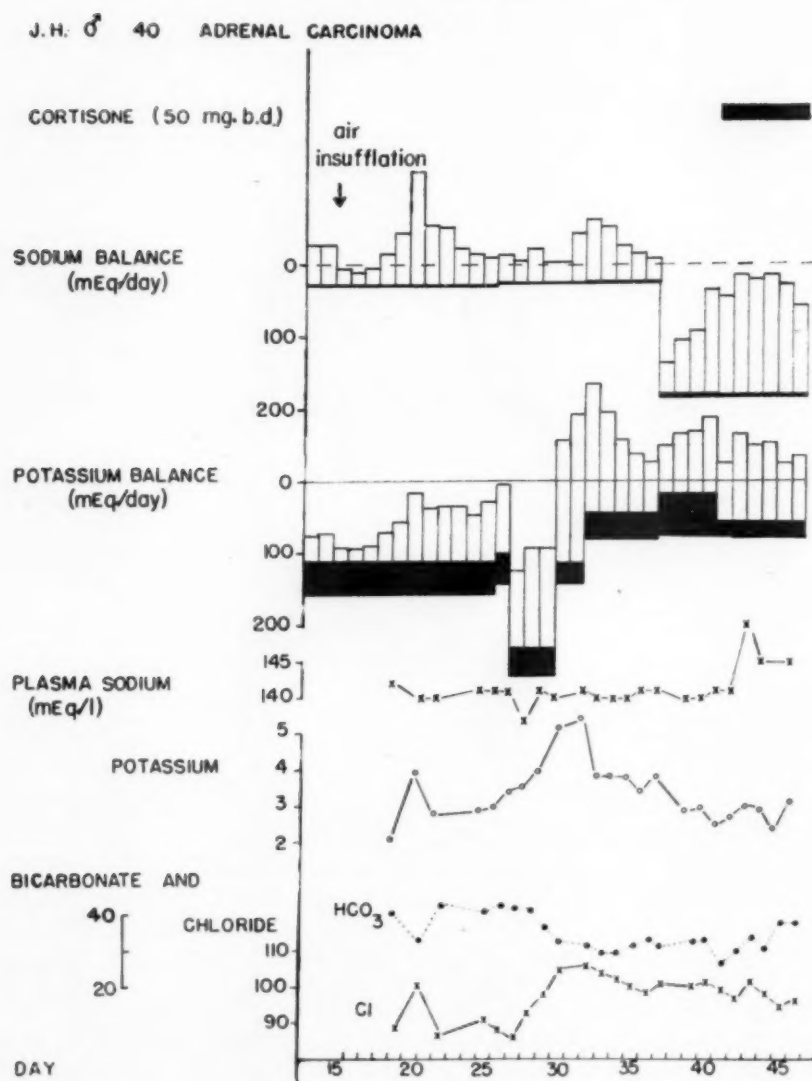


FIG. 3. Metabolic studies in Case 1. Balances of sodium and potassium. Plasma concentrations of sodium, potassium, bicarbonate and chloride are shown.

lowed by a normal balance for three days (days 15, 16, 17). During the next nine days (days 18 to 26) the sodium balance became spontaneously and markedly negative, the total deficit being 352 mEq. The urinary volume increased and the fluid balance was negative on four of these days (days 20, 21, 22 and 24). There was no overt change in the patient at this time, and his temperature and pulse were unaltered.

Potassium balance was positive throughout this phase (days 13 to 26). If the faecal output is assumed to be constant, the total gain was 762 mEq.

Plasma electrolyte concentrations in mEq./L. were on day 19, sodium, 142; potassium, 2.1; chloride, 89 and bicarbonate, 41. A striking brief return to normal values took place on day 21 when the sodium was 140; potassium, 3.9; chloride, 104 and bicarbonate, 32 mEq./L. On the previous day (day 20) the sodium balance had been -129 mEq. and the fluid balance -1720 ml. without any obvious change in the patient

or in his environment. A day later (day 22) the plasma electrolytes returned to their usual abnormal levels.

Second period (days 27, 28, 29): A high potassium diet of 270 mEq. per day was given by adding potassium chloride to the diet. The sodium intake remained low at 25 mEq. per day. The faecal sodium was 2 mEq. per day and the faecal potassium 41 mEq. per day. The sodium balance continued to be slightly negative, the total deficit for the three days being 32 mEq. The potassium balance became strikingly positive, a total of 307 mEq. being retained. The urinary potassium rose from 95 to 138 mEq. per day. The plasma sodium changed little. The plasma potassium rose sharply to reach 5.2 mEq./L. on the third day (day 29). This abrupt increase made it desirable to revert to the previous lower intake. On the third day the plasma chloride reached 105 mEq./L. and the bicarbonate fell to 33 mEq./L.

Third period (days 30 and 31): The diet was the

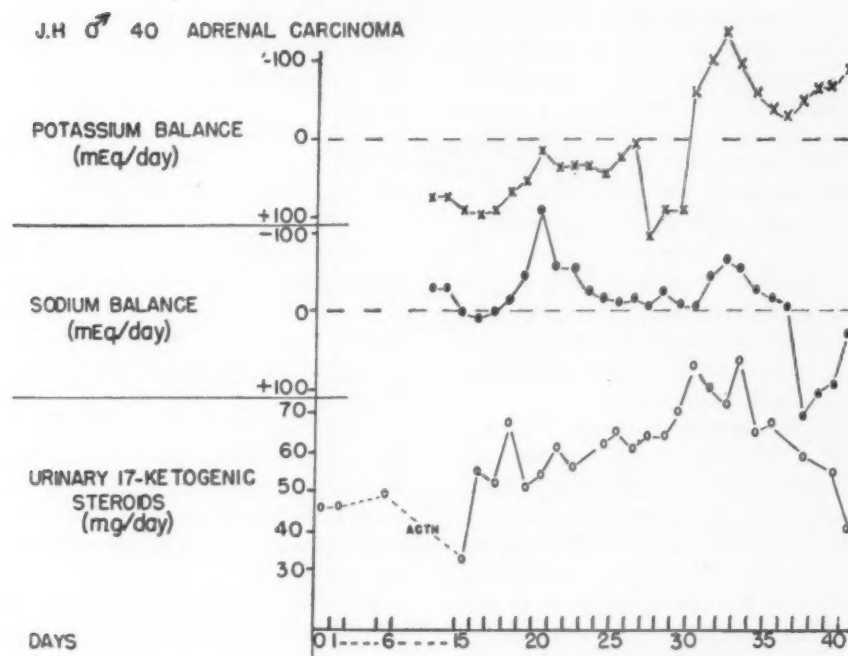


FIG. 4. Case 1. Line diagram of sodium and potassium balances, and of urinary output of 17 ketogenic steroids.

same as in the first period (sodium 25, potassium 141 mEq. per day). The sodium balance continued slightly negative, the total loss being 47 mEq. The potassium balance was negative, the total deficit being 151 mEq. The urinary potassium continued to increase to 193 mEq. per day. The plasma potassium was 5.4 mEq./L. on the second day.

Fourth period (days 32 to 36): A diet low in both sodium (25 mEq. per day) and potassium (80 mEq. per day) was now given. The faecal sodium was 4 and the faecal potassium 35 mEq. per day. The sodium balance was negative throughout, the daily urinary sodium showing a stepwise decrease from 82 to 30 mEq. The potassium balance also remained negative throughout, with a parallel stepwise decrease in the daily urinary potassium from 179 to 73 mEq. The total deficit was 350 mEq. The plasma potassium fell from 5.4 to 3.8 mEq./L. The other electrolytes showed small changes only.

Fifth period (days 37 to 40): The diet was high in sodium (184 mEq. per day) and low in potassium (78 mEq. per day). The faecal sodium was 6 mEq. per day, the faecal potassium 61 mEq. per day. The sodium balance became strongly positive, and there was a stepwise rise in urinary sodium from 30 to 144 mEq. per day. The potassium balance became increasingly negative, with a total deficit of 269 mEq. The plasma potassium fell further to 2.8 mEq./L. The other electrolytes remained virtually unchanged.

Sixth period (days 41 to 46): A diet containing 172 mEq. of sodium and 80 mEq. of potassium per day was given together with 50 mg. of cortisone twice daily orally. The faecal sodium was 3 mEq. per day and the potassium 16 mEq. per day. The sodium

balance remained positive with apparent gains (average 30 mEq. per day) greater than those usually due to insensible loss (10 to 15 mEq. per day) in this air-conditioned ward. The potassium balance was negative, the total deficit being 109 mEq. The plasma sodium rose to 150 and then fell to 145 mEq./L. The other electrolytes were unchanged.

TABLE I
EFFECT OF VARYING INTAKE ON SALIVARY SODIUM AND POTASSIUM

Days	Intake		Saliva (Means \pm S.E. *)		
	Na (mEq./day)	K (mEq./day)	Na (mEq./L.)	K (mEq./L.)	Na/K (mEq./L.)
19-26	28	159	7.3 \pm 1.1	39 \pm 1.3	0.19 \pm 0.025
27-29	25	270	6.8 \pm 1.6	43 \pm 3.0	0.16 \pm 0.029
32-36	25	80	6.9 \pm 1.6	38 \pm 2.6	0.18 \pm 0.042
37-40	184	78	7.5 \pm 2.2	34 \pm 2.2	0.22 \pm 0.059
41-46	172	80†	5.7 \pm 1.3	39 \pm 1.1	0.15 \pm 0.054

* Standard error.

† Plus cortisone 50 mg. twice a day.

Salivary electrolytes were determined at 10 A.M. on many days. On all occasions the saliva was viscid and was produced with difficulty. Its rate of flow was approximately 0.3 ml. per minute. The concentrations of sodium and potassium, the sodium/potassium ratio and the dietary intake of these ions are given in Table I.

The data depicted in Figure 4 appear to show a close relationship between potassium balance and the

urinary output of 17-ketogenic steroids. When this balance was positive, the output of steroids was greater than the base-line values (days 15 to 26). A further rise in steroid output followed the increased positive balance produced by administration of extra potassium (days 27, 28, 29). From day 30 onwards, the potassium balance was negative, and the urinary steroids fell to baseline levels, with the exception of a single rise on day 33.

It is notable that variations in sodium balance ran parallel with those in potassium balance, except when sudden changes occurred with supplementary potassium on day 26 and with sodium on day 36. These features are considered in the discussion.

Oral administration of cortisone in a dose of 50 mg. twice a day (days 41 to 46, Fig. 2) did not produce any reduction in urinary 17-ketosteroids, but there was the expected increase in 17-ketogenic steroids.

On April 13, 1955, operation was performed by Mr. R. W. Nevin, through a left loin incision with removal of the 12th rib. A very large tumour was found above the left kidney. The tumour extended towards the midline and surrounded the great vessels. A large part of it was removed and the left kidney had to be sacrificed. Twenty-nine days after operation the urinary output of 17-ketosteroids was 31.9 mg.; of 17-ketogenic steroids, 57 mg.; and of aldosterone, 6 μ g. per day. Following operation uraemia and left ventricular failure developed and the patient died five weeks later. Permission for a postmortem examination could not be obtained.

Pathologic report: The part of the tumour removed at operation and the left kidney were examined by Dr. J. L. Pinniger who reported a tumour of the adrenal gland which weighed 1,400 gm. with dimensions of 21 by 11 by 6 cm. The tissue had one uncut surface which showed a nodular appearance, the nodules being composed of soft yellowish tissues with small dark brown flecks in it. They were separated by strands of slightly darker brownish yellow tissue. The cut surface was extremely irregular but again was nodular, and was made up of yellow tissue with darker brown areas. On histologic examination the tumour was seen to be a well differentiated carcinoma of the adrenal cortex. The tumour was necrotic in places, and thrombi were present in the stromal blood vessels. The tumour cells on the whole were of regular size, but here and there giant forms appeared.

The left kidney weighed 200 gm. The outer surface was for the most part smooth. The capsule was fairly firmly adherent and the subcapsular surface of the kidney was fairly granular. On histologic examination the kidney showed preservation of its normal architecture. Apart from focal ischaemic changes due to arteriosclerosis, no glomerular lesions were present. There was a patchy deposition of calcium salts, principally present in the medulla, involving the wall of the collecting tubules. In some areas these led to destruction of the wall, and the presence of calcium salts

lying in the lumen and extending into the interstitial tissue. There was no specific abnormality of the proximal or distal tubules, apart from those due to ischaemic change.

A portion of the adrenal tumour weighing 742 gm. contained 10 μ g. of aldosterone, 250 μ g. of hydrocortisone and 10 μ g. of cortisone.

CASE II. Renal tubular acidosis: In January 1949, a man aged 29, an asphaltier, had a severe aching pain in the right loin which lasted for a week. He had previously been healthy. Three weeks after this episode polyuria and extreme thirst developed, and he drank 10 pints of water during the day and 6 pints during the night. He complained of a salty, metallic taste in his mouth and felt very weak. He became impotent. As an outpatient his urine was found to contain a small amount of protein, and a trace of reducing substances at a time when the blood sugar was 109 mg. per cent.

In April 1949 he was admitted to St. Thomas's Hospital. His thirst was then less intense, although he was still drinking 6 pints of water during the day and 3 pints during the night. He had been constipated for ten days. In the past year he had lost 12 pounds in weight. On examination he did not look ill. The heart, lungs and nervous system were normal; so was the abdomen except for a palpable descending colon. The blood pressure was 105/60 mm. Hg. His weight was 145 pounds (66 kg.). The urine had a specific gravity of 1.003 and contained a small amount of protein but no reducing substances. Radiologically, the chest, abdomen and skull were normal. The Wassermann reaction was negative. The haemoglobin was 100 per cent (Haldane) (14.8 gm. per 100 ml.).

During thirty-six hours without fluid the patient passed 1,800 ml. of urine, the highest specific gravity of which was 1.011. The blood urea was 90 mg. per cent, and the urea clearance was 25 per cent of average normal. Two intravenous pyelograms showed "no excretion of dye." A midstream specimen of urine revealed a trace of protein and numerous leukocytes, but it was sterile on culture. A twenty-four-hour specimen yielded no tubercle bacilli.

An intramuscular injection of 10 units of pitressin produced no change in the rate of urine flow or in the specific gravity (which was 1.008 before and after the injection).

Cystoscopy disclosed a normal bladder. Ureteric catheters were passed full distance without difficulty. Urine from these catheters contained: protein ++, pus cells ++, and epithelial cells; one granular cast was seen in the urine from the right kidney. On culture no ordinary pathogens or Myco. tuberculosis were grown. When retrograde pyelography was attempted, the right kidney was normal; the left catheter had slipped out of position.

The mannitol clearance was 26 ml. per minute and PAH clearance 28 ml. per minute. At this time the

AT 30 ♂ CHRONIC NEPHRITIS

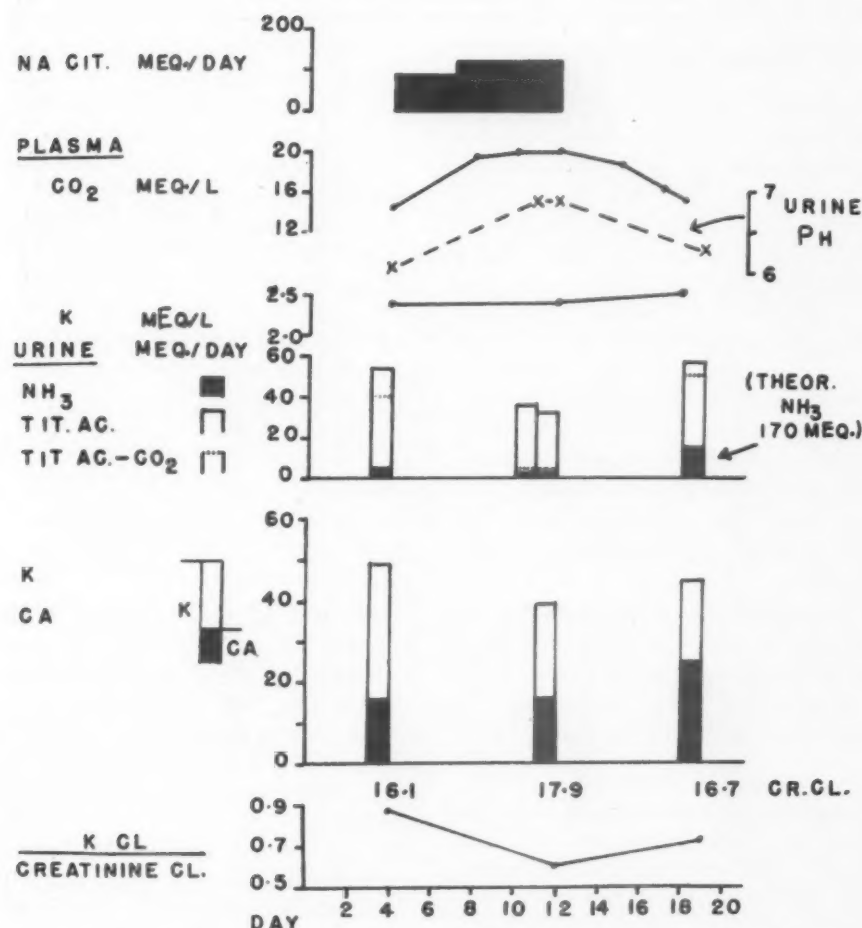


FIG. 5. Case II. The effect of sodium citrate on plasma potassium and bicarbonate; on the urine pH, ammonia, titratable acid, titratable acid minus bicarbonate, potassium and calcium output; and on the ratio of the renal clearances of potassium and creatinine.

blood urea was 72 and 83 mg. per cent on two separate days.

The patient was discharged from the hospital in May, 1949, and five days later was readmitted after a sudden attack of weakness of the legs and arms. For two days he had been vomiting and was again constipated. He was apathetic and dull, and unable to move either of his legs or his left arm. The limbs were flaccid, the plantar responses flexor. The tendon reflexes and sensation were normal. The blood pressure was 100/60 mm. Hg. The urine contained a small amount of protein and no reducing substances. The plasma bicarbonate was 10.2 mEq./L., the plasma chloride was 120 mEq./L. and the serum potassium, 1.3 mEq./L. The blood urea was 106 mg. per cent. The electrocardiogram showed flat T waves and prominent U waves. The patient was given 1.3 gm. (12 mEq.) of oral potassium citrate hourly for 10 doses. The following morning he was more alert

and able to move his limbs normally. Muscle potassium was 30 mEq. per 100 gm. of dry, fat-free muscle (normal 36 to 49 mEq.). He continued to take potassium citrate in doses of 2.6 gm. (24 mEq.) three times a day. On June 17 the plasma bicarbonate was 19.4 mEq./L.; the plasma chloride, 111 mEq./L.; and the serum potassium, 3.3 mEq./L. The blood urea was now 56 mg. per cent. The urinary volume was approximately 4 L. a day. The plasma calcium was 9.2 mg. and the phosphorus 3.4 mg. per cent. The patient was discharged from the hospital taking 2.6 gm. of potassium citrate daily.

During the next six months the patient was able to work although he complained of fatigue, backache, polyuria and thirst. The plasma potassium varied between 2.7 and 4.3 mEq./L., the dose of potassium citrate being varied as necessary. He was again admitted in January, 1950, after an attack of vomiting. The blood pressure was between 100/65 and 90/55

TABLE II
CASE II: URINARY OUTPUT OF AMMONIA, TITRATABLE ACID, TITRATABLE ACID MINUS CO₂;
EFFECT OF SODIUM CITRATE ON URINARY OUTPUT OF POTASSIUM AND CALCIUM

Day	Sodium Citrate (mEq.)	Plasma Concentrations			Urine						
		Bicarbonate (mEq./L.)	Chloride (mEq./L.)	Potassium (mEq./L.)	Vol. (L.)	pH	Ammonia (mEq.)	Titratable Acid (mEq.)	Titratable Acid Minus CO ₂ (mEq.)	Potassium (mEq.)	Calcium (mEq.)
4	0	15	105	2.4	4.20	6.07	5	54	41	49	16
8	90	19
10	120	20	107
11	120	3.78	6.89	3	36	4
12	120	21	110	2.8	4.15	6.89	3	32	3	39	16
15	0	19
17	0	17
18	0	16	110	2.6	5.56	6.30	15	57	50	45	25

mm. Hg. The plasma bicarbonate was 13 mEq./L.; the chloride, 110 mEq./L.; and the serum potassium, 3.4 mEq./L. Vomiting ceased spontaneously, and it was decided to reassess the patient's condition. As before he had the symptoms of weakness, thirst,

TABLE III
CASE II: RENAL CLEARANCES AND MAXIMAL TUBULAR EXCRETORY CAPACITY (PAH)
SODIUM CITRATE (56 MEQ.) AND POTASSIUM CITRATE (31 MEQ.) HAD BEEN GIVEN DAILY FOR SIX DAYS

Periods (of approximately 20 min.)	Renal Clearance (ml./min./1.73 sq. M.)					T _{mp} PAH	Clearance Ratio Potassium/Inulin
	Inulin	Urea	Creatinine	Potassium	PAH		
1	21.7	20.7	23.4	14.2	0.66
2	23.2	21.7	26.4	15.3	0.66
3	19.7	25.9
4	20.2	28.4
5	21.8	25.2	2.5	...
6	18.8	21.5	0.7	...

polydipsia, polyuria, and the unpleasant metallic taste in the mouth. His weight was 128 pounds (58.2 kg.). The temperature and pulse rate were normal. There were no abnormal physical signs in the cardiovascular, respiratory, gastrointestinal or central nervous systems. The blood pressure was 100/65 mm. Hg. The haemoglobin was 64 per cent (Haldane). The red blood cells were 3.3 million per cu. mm.; the leukocytes were 11,000 per cu. mm. with a normal differential count. The urine contained protein ++, no reducing substances and no abnormal deposit. The daily volume of urine was nearly 4 L. The blood

urea was 85 mg. per cent. While the patient was taking 1.3 gm. (12 mEq.) of potassium citrate three times a day, the plasma electrolytes were, in mEq./L.; potassium, 3.4; bicarbonate, 13; and chloride, 110. The plasma calcium was 9.0 mg. per cent; the phosphorus, 3.5 mg. per cent; and the alkaline phosphatase, 3.3 Shinowara units. Radiologically the skeleton was normal.

An attempt was next made to determine whether or not the kidneys were intrinsically responsible for the loss of potassium and for the acidosis, and whether or not potassium was being excreted specifically or merely as a base. The investigation was planned in three phases (Fig. 5 and Table II): during the first phase (days 1 to 4) all medicines including potassium citrate were withdrawn; during the second phase (days 5 to 12) sodium citrate was given orally in doses of 90 mEq. per day for the first three days, and then 120 mEq. daily for the next five days; during the third phase all medicines were withdrawn again for six days. At the end of each phase the concentrations of potassium and bicarbonate in the plasma were measured. The pH, ammonia, titratable acid, titratable acid minus carbon dioxide, and potassium and calcium were determined in twenty-four-hour specimens of urine collected and kept on ice and under a thick layer of toluene (Table II). The creatinine clearances were also calculated.

Figure 5 shows that the plasma potassium was virtually unchanged throughout the investigation. When sodium citrate was given, the plasma bicarbonate rose from 15 to 21 mEq./L., and the pH of the urine increased from 6.07 to a maximum of 6.89. Both the plasma bicarbonate and pH levels had returned to their previous levels by the end of the investigation.

Renal production of ammonia and of titratable acid, and the value for titratable acid minus bicarbonate were greatest on day 18, being 15, 57 and 50 mEq. per day, respectively. At the end of phase 2, during which sodium citrate was given, the value for titratable acid minus bicarbonate was only 4 and 3 mEq. per day (days 11, 12).

The urinary potassium and calcium were also at their lowest at the end of phase 2, but it is notable that calcium excretion was also low at the end of phase 1 (day 4). The clearances of creatinine showed little change during the investigation, being 16.1, 17.9 and 16.7 at the end of each phase, respectively. The ratio of the clearances of potassium and creatinine were highest when the patient was most acidotic.

Other renal function tests were repeated and extended. Following the previous investigations the patient was given 6 gm. (56 mEq.) of potassium citrate and 3 gm. (31 mEq.) of sodium citrate daily for six days. The renal clearances of inulin, urea, creatinine, potassium and PAH were measured over periods of approximately twenty minutes in duration. The T_{mPAH} was also determined. The results are shown in Table III. The plasma potassium was 2.6, bicarbonate 18 mEq./L. Cutler's test for renal conservation of chloride was then performed; on the third day urinary chloride concentration was 20 mEq./L. which is well within normal limits.

The patient was now feeling relatively well; his blood urea was 71 and 92 mg. per cent; he was discharged from the hospital taking a mixture of sodium (31 mEq./day) and potassium (56 mEq./day) citrates. As an outpatient, he continued to have polyuria, polydipsia and weakness. In December 1950 he was readmitted after two days of severe diarrhoea of abrupt onset; he was weak and severely dehydrated. Temperature was 99°F., blood pressure 95/60 mm. Hg. Haemoglobin 60 per cent (Haldane) with a mean corpuscular haemoglobin concentration of 27 per cent. The abdomen was distended and there was mild generalized tenderness. There were no abnormal physical signs. Plasma electrolytes (mEq./L.) were: sodium, 141; potassium, 2.5; chloride, 124; bicarbonate, 9; and blood urea 81 mg. per cent. The dehydration responded slowly to intravenous and intragastric infusions.

Meanwhile culture of the faeces showed no pathogens, but one to three stools were passed daily; the abdomen persistently distended and felt doughy. There was pyrexia of 100 to 101°F. each evening. No abnormal physical signs were present elsewhere, urine culture was sterile, and the possibility of tuberculous enteritis or peritonitis was considered. Examination of faeces for Myco. tuberculosis was negative; culture again showed no pathogens. The fat content of dried faeces was 40 per cent. X-ray of the chest showed no abnormality, while x-ray of the abdomen revealed coarse speckling of the renal areas consistent with nephrocalcinosis. Anaemia persisted in spite of oral

and intravenous iron therapy but there was symptomatic improvement sufficient to allow the patient to return home.

In the next four months he took up to 16 gm. of potassium citrate daily, plasma potassium varying from 3.0 to 3.7 mEq./L.

In May 1951 the patient was admitted for the last time complaining of diarrhoea and vomiting. He was cachectic and anaemic. He had an eroding gingivitis and a marked foetor. The blood pressure was 95/65 mm. Hg. The blood urea was 85 mg. per cent., the plasma bicarbonate, 12 mEq./L.; the chloride, 118; the potassium, 2.4; and the sodium, 124 mEq./L. The urinary output fell and the patient slipped into coma, dying two and a half years after the onset of his symptoms.

Postmortem examination revealed the kidneys to be both much reduced in size and very pale; the capsules stripped with great difficulty; the cortex was a mere rind. There was nephrocalcinosis in the medullae of both kidneys; small renal calculi were present in the calyces; projecting from almost all the renal papillae were deposits of calcified material. The pleural cavities contained 1½ pints of blood-stained fluid. The peritoneal surface of the small intestine was discoloured and gray; no gross haemorrhages of ulcers were noted. The mesentery was oedematous; enlarged glands were observed with pin-point dots on the cut surface.

Sections of kidney showed destruction of normal architecture with crowding of the glomeruli and a marked increase of interstitial tissue. The principal glomerular abnormality was concentric fibrosis around Bowman's capsule. The majority of glomeruli showed this change, and many had progressed to fibrotic replacement of the glomerular tuft. The tubules showed varying degrees of degeneration. The distal tubules appeared to be more severely affected, and were often difficult to identify in the interstitial tissue, which was heavily infiltrated by many inflammatory cells. There was a patchy deposition of calcium salts in the cortex and medulla. These deposits were mainly in the interstitial tissue, although they often involved the wall of the tubules, and in some areas disrupted the tubules and lay in the lumen. In the medulla the deposits sometimes attained large size and had the appearance of small calculi. There was considerable fibrosis and chronic inflammatory cell infiltration in these areas.

Numerous healed granulomata were found in chronically inflamed and very damaged and fibrosed mesenteric lymph glands. The liver and spleen contained numerous, mainly periportal, miliary granulomata. The lungs showed confluent bronchopneumonia and a few granulomas scattered throughout the lungs.

Diagnosis: Generalised miliary granulomatosis (Boeck's sarcoidosis).

CASE III. This man aged fifty-two, a solicitor, was admitted to the Royal South Hants Hospital in

February, 1955, complaining of periodic attacks of bronchial asthma since 1942, of nocturnal polyuria for thirteen years, and of high blood pressure for ten years. In 1940 he joined the Army and was considered medically fit. In mid-1942 he noticed that he had to pass urine frequently during the night. This symptom grew in severity, and in the two years prior to his admission he found that he lost 5 pounds in weight between going to bed and getting up, urine being passed four or five times each night. No polyuria occurred by day, and he noticed that if he drank 2 pints of beer at midday there was a three hours' delay before the onset of diuresis. In September 1942, the patient had his first attack of bronchial asthma which lasted for about a week. Several attacks followed during the next two years. In September 1944 the patient appeared before a medical board, was found to have hypertension, and was boarded out of the Army. The hypertension worried him very little. He had occasional headaches, but before the war suffered from migraine. Since 1943 the patient had noticed waning potency, which was progressive. In May 1945 a left facial palsy developed from which he recovered in three days. It is not certain whether this was due to an upper or lower motor neurone lesion. In 1947 the patient suffered from a severe attack of pain in the left loin, and in 1949 had infective hepatitis.

On examination, the patient was seen to be heavily built and rather obese. There were no striae. The blood pressure was 240/170 mm. Hg. The aortic second sound was accentuated but the heart was not obviously enlarged. The jugular venous pressure was normal. On examination of the chest there was a little diminution in the breath sounds at the left base, and on radiologic examination a small pleural effusion was present. The abdomen and nervous system were normal. Only early hypertensive changes were present in the retinae.

The patient was transferred to St. Thomas's Hospital where the following investigations and biochemical studies were undertaken.

The plasma sodium was 140, the potassium, 2.7; the chloride, 98; and the bicarbonate, 41 mEq./L. The pH of the blood was 7.35.

The blood urea was 60 mg. per cent. The urine contained a small amount of protein. On microscopy occasional leukocytes were seen, and on culture there was a poor growth of enterococci. These findings were confirmed on subsequent occasions.

After thirty-six hours without fluid, the urinary specific gravity was 1.011. The patient then drank 1,600 ml. of water and passed 80 ml. of urine in the next four hours. During six days the urinary volume from 10 A.M. to 10 P.M. averaged 550 ml., and from 10 P.M. to 10 A.M., 1,540 ml. His weight at 10 P.M. averaged 2.0 kg. higher than at 10 A.M.

An intravenous pyelogram showed normal excretion from the right kidney which was normal in appearance. There was no convincing evidence of excretion from the left kidney.

On day 11 (*vide seq.* and Fig. 6), when the patient's intake of potassium was only 17 mEq. per day, and his plasma potassium was 2.3 mEq./L., the following renal clearances were obtained (ml. per minute): inulin, 64; PAH, 267; phosphorus, 21; potassium, 48; the inulin/PAH ratio was 0.24 and the potassium/inulin ratio 0.75.

The urinary output of 17-ketosteroids was 19.5, 12.8 and 13.5 mg. on successive days, and of 17-ketogenic steroids 11.5, 14.5 and 8.8 mg. on the same days. ACTH gel (a batch which was subsequently found to be not very active) in a dose of 20 units was then injected intramuscularly twice daily for four days (days 4 to 7, Fig. 5), on which the urinary output of 17-ketosteroids was 18.7, 10.0, 14.6 and 15.3 mg. and of 17-ketogenic steroids 28.7, 28.4, 22.7 and 22.7 mg.

The urinary aldosterone was 1.5 and 1 μ g. on days 1 and 2 when his sodium intake had just been raised from approximately 30 to 124 mEq./day. The plasma hydrocortisone on day 4, before the administration of ACTH was 6.7 μ g. per 100 ml.

The salivary sodium/potassium ratio on three occasions was 0.15, 0.13 and 0.12, the flow rate being 0.85, 0.94 and 0.170 ml. per min., respectively.

The haemoglobin was 109 per cent (Haldane). The leukocyte count was 3,000 per cu. mm. with a normal differential distribution. The erythrocyte sedimentation rate was 5 mm. in one hour (Westergren).

Electrolyte balance (days 1 to 30, Fig. 6). Prior to his admission the patient had taken a low salt, low-calorie diet for several years. On day 2 the sodium intake was increased to 124 mEq. per day by the daily addition of 85 mEq. of sodium chloride. This intake was kept approximately constant during the investigations, while the potassium intake was varied. The calorific value of the diet was kept low at 970 calories per day in order to reduce the patient's weight.

On the baseline days (days 2 and 3), the urinary sodium was 17 and 63 mEq., and 84, 84, 114 and 102 mEq. when ACTH was given (days 4 to 7), the balance being positive. On the following two days (days 8 and 9), the urinary sodium was 179 and 154 mEq., the balance being negative. Thereafter the sodium balance behaved normally; there was no indication of any unusual tendency to retain sodium. A brief retention appeared when the potassium intake was lowered (days 11 to 13), and a brief diuresis when potassium intake was raised (days 17 to 19). There was also a brisk diuresis when ammonium chloride was administered (days 27 to 31). The faecal sodium varied from 4 to 6 mEq. per day.

The balance of potassium was negative during the administration of ACTH (days 4 to 7) and for the next two days (days 8 and 9). When the intake of potassium was reduced to 17 mEq. per day (days 10 to 16), a value only just higher than the faecal loss of 15 mEq. per day, the potassium balance became strongly negative, with no tendency after the first two days for the urinary potassium to fall. From day 4 to day 16, the total potassium balance was minus 387 mEq.

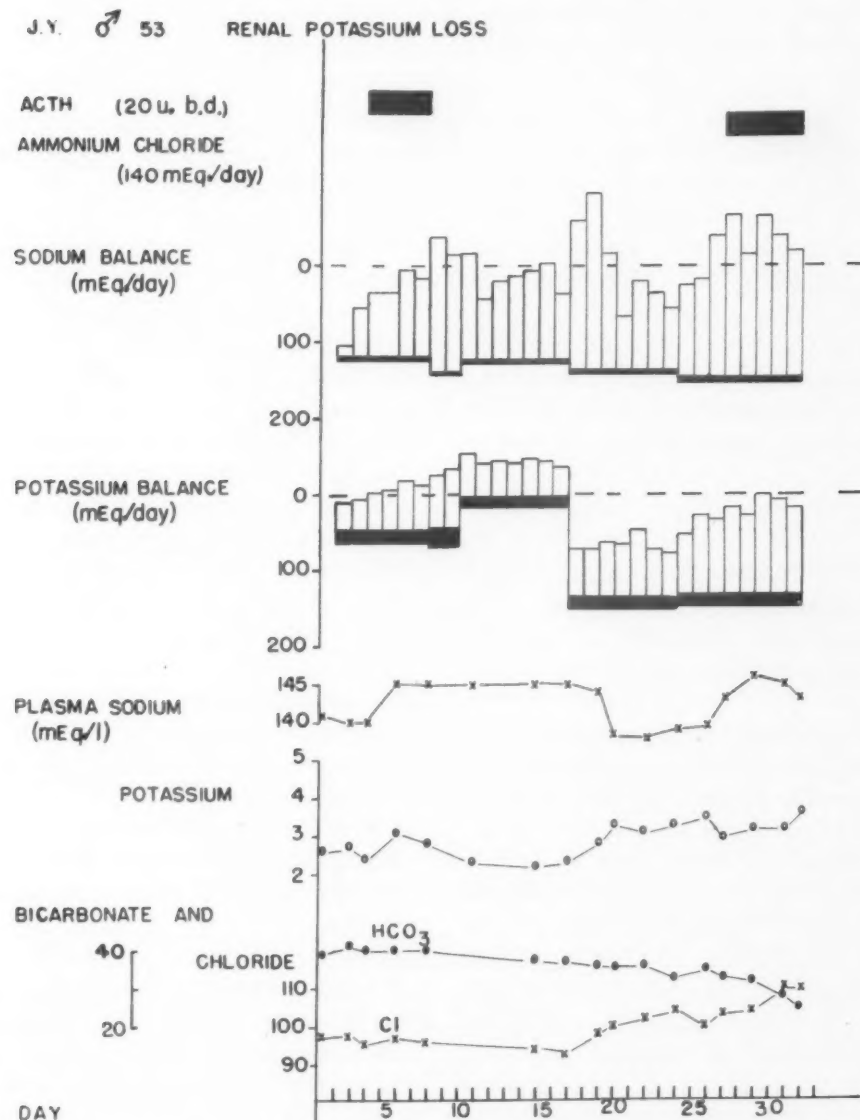


FIG. 6. Metabolic studies in Case III. Balances of sodium and potassium. Plasma concentrations of sodium potassium, bicarbonate and chloride are shown.

On day 17 the intake of potassium was increased to 150 mEq. per day. The faecal potassium was 15 to 17 mEq. per day. The urinary potassium rose slowly, and there was considerable retention of potassium, even when ammonium chloride was administered. The total retention from day 17 to day 31 was 647 mEq. The patient had gained 260 mEq. of potassium during his stay in hospital.

The plasma sodium rose from 140 to 145 mEq./L. during the administration of ACTH. It then remained constant until the intake of potassium was increased on day 17. Three days later it had fallen to 138 mEq. and it remained at this level until day 27.

The plasma potassium varied between 2.2 and 3.1 mEq./L. until the intake of potassium was raised on day 17. Three days later it was 3.3 mEq./L. and thereafter varied between 3.0 and 3.6 mEq./L. The lowest limit of normal in this laboratory is 3.5 mEq./L.

The plasma bicarbonate varied between 37 and 41 mEq./L. until the supplement of potassium was given; it then fell slowly to 33 mEq. until ammonium chloride was given, whereupon the fall continued to 25 mEq./L.

The plasma chloride was originally 97 mEq./L., falling to 93 mEq./L. on day 17. After administration of potassium chloride, it rose to 103 mEq. on day 27. Ingestion of ammonium chloride was followed by a further rise to 110 mEq./L.

The blood pH on day 2 was 7.35. Before ammonium chloride was given on day 27 it was 7.32, and after five days' administration of ammonium chloride it was 7.35.

Presacral air insufflation showed both adrenals to be normal, although the left was a little larger than the right. An intravenous pyelogram showed practically no excretion of dye by the left kidney.

Laparotomy was not performed on this patient, for reasons which will be discussed. He was discharged from the hospital.

COMMENTS

Renal Loss of Potassium. The normal kidney reduces its excretion of potassium to between 3 and 15 mEq./day when potassium deficiency is experimentally produced, even in the presence of acidosis or alkalosis [13-17]. These studies were of short duration, lasting four to eleven days [15]. The two patients of Schwartz and Relman [18] who had prolonged potassium deficiency, from the overuse of laxatives, also reduced their urinary excretion to 3 and 7 mEq./day.

A reasonable criterion for the renal loss of this ion would therefore appear to be the continuous daily excretion of more than 20 mEq./day when the plasma potassium is below normal. This would not exclude the possibility of positive balance providing potassium intake were sufficiently high.

All three cases reported here show such an abnormality. In Case I (Fig. 3) the lowest excretion rates were 22, 16 and 22 mEq./day on days 15, 16 and 17, and the lowest average for six consecutive days (13 to 18) was 35 mEq./day; plasma potassium was below 2.5 mEq./L. In Case II the urinary potassium was greater than 39 mEq./day on days 4, 12 and 18 (Fig. 5) when plasma concentration was below 2.6 mEq./L. In Case III (Fig. 6) the urine potassium content fell to an average of 46 mEq./day when potassium intake was reduced in order to test the renal ability to conserve this ion (days 10 to 16); plasma potassium was below 2.3 mEq./L. at this time.

Potassium deficiency is indicated in all three cases by evidence other than hypopotassaemia; Cases I and III retained 1,069 and 260 mEq., respectively while on balance studies, and in Case II, in which such studies were not possible, there was the clinical evidence of muscle paralysis, low muscle potassium, and cure with administration of potassium salt. Faecal potassium was abnormally high in Case I and undoubtedly contributed to the deficiency, but the striking feature was the continuously high urinary potassium which produced negative balance when potassium intake was lowered from high to normal levels on day 32.

The possible causes for renal potassium loss lie either in the renal tubule itself or in its control by hormones of the adrenal cortex. Case I is an

example of deranged control of electrolyte excretion by hormones from a carcinoma of the adrenal cortex; his urine contained excess 17-ketosteroids, 17-ketogenic steroids and aldosterone but his plasma hydrocortisone concentration was only at the upper limit of normal.

Since Conn [4,5] described a case of potassium deficiency due to renal loss which was caused by an aldosterone-producing tumour of the adrenal cortex, and successfully predicted that a similar tumour was likely in a case which had been published as an example of potassium-losing nephritis [19], several cases have been regarded as examples of the syndrome which he called "primary aldosteronism" [19-29] (Table IV) besides six others personally communicated to Conn and Louis [30]. In some of these cases, however, it has not been possible to search for direct evidence of excess production of aldosterone [21,23,26,28]; more important, two patients, clinically similar, showed normal values for this hormone in urine [22,25] whilst in a third [20] who had one raised urine value there were also two normal values for both blood and urine aldosterone.

Prunty [31] called attention to this aspect of the problem and observed that the causes of this clinical condition were more complex than the production of excess aldosterone by benign adrenal cortical tumours. Thus hypokalaemia and alkalosis are often found in manifest Cushing's syndrome; three cases of this condition have been recorded in which excess sodium-retaining material [32] or aldosterone [33] has been found; in the cases of the latter authors the urine contained 51 μ g. per day. The electrolyte abnormalities also occur during therapy with cortisone or with ACTH, although current evidence [34] suggests relatively small transitory increases of aldosterone output when ACTH is given.

In the recent cases the causative lesion varied: in those of van Buchem [27] and Wyngaarden [26] there was hyperplasia of the adrenal cortex and no tumour was present. In the case of Foye and Feichtmeir [29] there was an adrenal carcinoma and, after temporary alleviation by removal of the tumour, there was a relapse with the appearance of metastases; in our Case I primary adrenal carcinoma was also present. In the case of Spaulding *et al.* [28] there were secondary deposits of bronchogenic carcinoma in the adrenal cortex. In the other cases, it was shown that localized tumours of the adrenal were present.

TABLE IV
URINARY OUTPUT OF ADRENAL STEROIDS PER DAY

Reference	Sex	Adrenal Lesion	17-keto-steroids (mg.)	17-keto-genic-steroids (mg.)	17-hydroxy-steroids (mg.)	11-oxy-steroids (mg.)	Corticoids (mg.)	Hydro-cortisone (μg.)	Sodium Retain-ing Steroids: Bioassay	Aldosterone (μg.)
			(5 to 21)*	(5 to 18)	(1 to 12)	(0.5 to 1.5)		(23 to 57)	†	†
[4,5]	F	Localised tumour	5.7	5.0	4 to 30 × normal
[79]	F	Localised tumour	normal	increased
[20]	F	Localised tumour	21 to 40	$\begin{cases} 0.7 \times \text{normal} \\ 1 \times \text{normal} \\ 2.3 \times \text{normal} \end{cases}$
[27]	M	Localised tumour	17.2	6.5	4.5
				5.8
[22]	F	Localised tumour	7.4	18.6	normal
			6.7	15.5
[23]	F	Localised tumour
[24]	F	Localised tumour	10 to 14	34 to 41‡	definitely increased
[25]	F	Localised tumour	6.0	10.7	normal
			5.9	11.4
[26]	M	Hyperplasia
[27]	M	Hyperplasia	12	4	4 × normal
[28]	M	Secondary carcinoma	4 to 7	8 to 12§
[29]	M	Primary carcinoma	6 to 15	25 to 60	2.4 × normal
Present			$\begin{cases} 10 \times \text{normal} \\ 10 \times \text{normal} \\ 15 \times \text{normal} \end{cases}$
Case I	M	Primary carcinoma	25 to 53	46 to 86

* Figures in parentheses represent the normal values.

† Since different assay methods give different normal values, results are quoted in relation to each author's normal value.

‡ "Blue tetrazolium reducing" steroids: these values considered to be definitely increased.

§ Dinitrophenylhydrazine method: normal range stated to be 1.5 to 3.

In Table IV it will be seen that, although the data are somewhat scanty, there appear to be patients in whom there was an increased excretion of steroids other than aldosterone. This is especially noticeable in the patients with primary carcinoma. It is remarkable that none of these particular patients, including the one in our present Case I, showed the usual appearances of Cushing's syndrome.

In Case I of this paper, the raised production of steroids other than aldosterone may account for differences from Conn's clinical and metabolic findings. The common features are hypertension, abnormally high secretion of sodium-retaining steroid, potassium deficiency with hypokalaemia and alkalosis, and hyposthenuria; the alkalosis and hyposthenuria being ascribed to the potassium deficiency [18]. Outstanding differences are that our patient (Case I) had oedema, an exceptionally high faecal potassium, and that his plasma potassium rose sharply to above normal concentration when the potassium supplement was given, whereas in Conn's case it could only be raised to low normal values. It is suggested [35] that this rapid increase may be more typical of increased adrenocortical activity and may reflect a diminished tendency for potassium to enter cells. When plasma potas-

sium reached normal values the plasma bicarbonate and chloride also returned to normal; they remained so to the end of the study although plasma potassium subsequently fell to the original level and potassium balance became negative.

A notable feature of the balance data (Fig. 4) is the parallelism between the sodium and potassium balances. There is a marked tendency throughout for variations in these to move in the same direction, except when there are sudden changes in over-all balance which were produced by supplementary potassium chloride on day 26 and by supplementary sodium chloride on day 36. Luetscher and Curtis [36] have shown that, in normal circumstances, reduction of sodium intake leads to increased aldosterone production while increased intake leads to a fall. If this occurred in Case I, urine potassium might be expected to be raised during the phase of low sodium intake, and lowered when the sodium supplement is given; in fact the reverse is true.

These observations are in contrast to the well known effect of single adrenal steroids including aldosterone [37] and can be observed in Conn's data [4] at times when his patient's output of 17-hydroxysteroids was changing rapidly as the result of withdrawal of administered hydro-

cortisone or ACTH. It also appears in the data of Foye and Feichtmeir [29] which had raised excretion of 17-ketogenic steroid, and Mader and Iseri [24] produced sodium diuresis in their case with intravenous cortisone. It is probable that the "glucocorticoids" are partially correcting an electrolyte abnormality induced by sodium-retaining steroid, similar to the antagonism between cortisone and DOCA shown by Forsham *et al.* [38] and Rosenbaum *et al.* [39]. A point in favour of this concept is the abrupt decrease of faecal potassium when cortisone was administered in Case 1.

In this case, there is an interesting association between the potassium balance and the 17-ketogenic steroid output (output of 17-ketosteroid paralleled that of 17-ketogenic steroids but is not charted for the sake of clarity). During the period of mild positive balance (days 13 to 26) there was a slow rise in the steroid output; when the balance was made strongly positive with supplementary potassium (days 27 to 29) there followed a sharp rise in steroid excretion which changed to a continuous fall when potassium balance became negative. The changes in steroid excretion appeared to follow from one to three days after changes in the balance, so that the possibility arises that positive potassium balance caused a rise in steroid output and that negative balance produced a fall; it is recognised that this is not a normal sequence.

It is notable that, although the expected effect of aldosterone is to produce a loss of potassium and a gain of sodium, this trend could be reversed in most of those cases in which balance studies have been performed. Thus, in Conn's case [4] potassium was retained during four of five days of supplementary dosage although there was evidence of resistance to repletion; in the cases of Evans and Milne [19], Milne and Muehrcke [22], Chalmers *et al.* [20], Mader and Iseri [24], and in our present Case 1 several hundred mEq. of potassium were retained when the intakes were high. In the opposite direction, sodium loss was seen in Mader and Iseri's case [24] when the intake was 34 mEq./day; the prolonged sodium loss in Case 1 when intake was 30 mEq./day may not be unusual, although Bartter [34] postulated that such patients should have an excessively low sodium output when the intake is reduced.

A possible cause for sodium loss in this patient is the apparently selective damage to the renal tubules presumably due to the potassium defi-

ciency; filtration rate was at the lower normal limit while the tubules' ability to handle water was considerably diminished. It is possible that, in this situation, the load of sodium presented to the tubules exceeds the ability of the tubules to reabsorb it so that urinary sodium could not be reduced below a maximum, which was not low enough to achieve balance.

The salivary Na/K ratio (Table 1) is at the lower normal limit (*vide seq.*) and is not significantly influenced by changes in electrolyte intake or balance, perhaps because the salivary glands were conserving sodium maximally throughout.

With regard to the preoperative problem of the precise nature of the lesion involved, although the evidence of a palpable abdominal tumour, together with the indications of renal displacement and a suprarenal tumour given by the intravenous pyelogram and air insufflation, was conclusive, the results of functional tests to decide whether or not the lesion was autonomous were equivocal. There was an undoubted increase in the output of ketogenic steroids and ketosteroids due to the administration of ACTH; it was not as great as the increase expected in patients with hyperplastic adrenals [37]. This appears to be the second instance of responsiveness of a carcinoma to ACTH [40]. On the other hand, cortisone did not suppress ketosteroid excretion.

Case 11 appears to be an example of renal loss of potassium due to inability of the tubules to produce ammonium ion, leading to excretion of potassium as fixed base. Ample evidence of gross tubular dysfunction, more severe even than the diminution of glomerular filtration, is provided by the inability to concentrate the urine in response to dehydration or to pitressin, by the occasional glycosuria, and by the inadequate tubular capacity to excrete PAH. Nevertheless, the results of Cutler's test demonstrated a normal conservation of chloride and, by inference, of sodium [41]. It is important that the renal production of titratable acid was normal, while that of ammonium ion was grossly inadequate; this would seem to preclude the possibility that the potassium loss was primary since, if that were so, production of titratable acid would be reduced while that of ammonia would be normal [16]. Additional support for the proposition that potassium loss is secondary to the inability to form ammonium is provided by the sparing effect of administered sodium citrate on the urinary loss of potassium and possibly calcium.

Albright and Reifenstein [42] consider that the acidosis and nephrocalcinosis are typical features.

Foss, Perry and Wood [43] have concluded that many cases of this type are initiated by congenital defects of tubular function. In view of the autopsy finding suggesting the presence of sarcoidosis, the possibility that this condition produced the nephrocalcinosis has to be considered. The clinical features in the penultimate hospital admission suggested the development of a tuberculous lesion at this time; this suggestion could not be confirmed. Nephrocalcinosis was already evident on x-ray films of the abdomen, and renal damage was of many months' duration. It has been pointed out [44] that secondary renal lesions may develop in sarcoidosis at a time when clinical evidence of the primary condition is almost entirely absent. Nevertheless, nephrocalcinosis in sarcoidosis appears to be regularly associated with hypercalcaemia which was repeatedly found to be absent in this case.

Case III illustrates the difficulties of ascribing renal loss of potassium to defects of the renal tubule or to their hormonal control. With regard to the former possibility, it has been suggested [45-49] that chronic pyelonephritis or hypertension may produce such defects. However, the situation is complicated by these factors: (1) potassium deficiency alone may produce renal damage [18]; (2) when the potassium loss is of hormonal origin, hypertension is usually present; and (3) the damaged kidneys may be liable to infection [22]. It is this complex interaction of possibilities which causes confusion. Evans and Milne [19] and Russell *et al.* [25] who originally ascribed the abnormalities of their patients to pyelonephritis have since shown these abnormalities to be due to adrenal tumours.

The features of hypokalaemia and alkalosis, potassium deficiency, hypertension and renal damage in this case could reasonably be ascribed to either cause. A special point in favour of a primarily adrenal pathology was the Na/K ratios in the saliva. These were low in comparison with normal values reported by Prader *et al.* [50] who also observed that the ratio increases with rising salivary flow and varies with time of day. However, Pawan [51] has reported a normal range of 0.15 to 2.10 (mean 0.58), and normal controls under our conditions gave ratios between 0.16 and 1.21 (mean 0.43; standard deviation ± 0.27) not consistently affected by the rate of salivary flow; the difference between

these groups is probably accounted for by diurnal variation, our collections being made between 10 and 11 A.M. It was not considered that the low ratio of 0.12 achieved in Case III was decisive.

It is unfortunate that negative findings are not to be relied upon: thus this patient had normal aldosterone excretion but this does not rule out primary adrenal dysfunction, as has already been noted. The air insufflation did not demonstrate a definite increase in adrenal size, but this would not be expected in hyperplasia and tumours could be so small that they might not be visualised by this method. Against the possibility of this patient's condition being of adrenal origin was the previous history of renal pain, the poor excretion of contrast medium by the left kidney, and the positive urine culture. The urinary excretion of 17-ketosteroids and 17-ketogenic steroids was normal and the response to ACTH was also thought to be normal. There was therefore no direct evidence to implicate the adrenal cortex but the final proof of operative exploration is lacking. In addition there was a prolonged positive potassium balance on normal intake in the presence of normal sodium intake.

The position is ably considered by Aird, Milne and Muehrcke [52] who concluded that primary adrenal abnormality "can only be excluded with absolute certainty by planned exploration of the adrenals or by necropsy."

In the light of these conflicting issues, the management of the case was considered. On the one hand were the possibilities that operative removal of an adrenal abnormality might reverse renal damage due to continued potassium deficiency, and might relieve hypertension. On the other hand were the absence of reasonable confidence in the possibility of adrenal abnormality, the risks of operation in a poor subject, the ease of correction of potassium deficiency by the administration of potassium salts, the possibility of removing the urinary infection with antibiotics, the probability that the longstanding hypertension had produced permanent renal damage, and finally the doubt whether permanent relief of hypertension was altogether desirable under these circumstances, while trial could be made of controlling it with hypertensive agents. With regard to this last consideration, it is noteworthy that Evans and Milne [19], Chalmers *et al.* [20] and van Buchem *et al.* [27] reported considerable decrease in renal function

when hypertension was relieved by removal of a tumour or hyperplastic adrenals.

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ADDENDUM

In Case III the patient died twenty-one months after discharge. An autopsy was performed by Dr. R. A. Goodbody who reported that congestive cardiac failure was the cause of death. Both adrenals were enlarged, one weighed 18.5 gm. and the other 15.5 gm. There was a yellow tumour, 20 mm. in diameter, in the cortex of the former. The kidneys, macroscopically, showed fine subcapsular granulation and the histology was consistent with malignant hypertension. A sample of muscle taken from the thigh contained 78 mEq. of potassium per kg. of fresh muscle (normal 77 to 103 mEq.).

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Glycinuria, a Hereditary Disorder Associated with Nephrolithiasis*

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SINCE the discovery of cystine in a bladder stone by Wollaston [7] in 1805, excessive amino acid excretion in the urine has been the subject of intensive investigation. The study of separate amino acids in urine has been greatly facilitated by the application of paper chromatography by Dent [2] in 1946. By this method specific patterns of urinary amino acid excretion, associated with various known syndromes, could be defined and new aminoacidurias were discovered. In the present communication we report a new aminoaciduria: glycinuria, which was detected by chromatographic examination of the urine from a patient with recurrent bilateral nephrolithiasis. Investigation of the family showed this aminoaciduria to be a hereditary disorder, associated with nephrolithiasis.

CASE REPORT

S. R., a twenty year old unmarried female dress-maker, born in Bulgaria and residing in Israel eight years, was admitted to the medical department on November 1, 1955, with a chief complaint of pain in the right lumbar region. At the age of two she had had fever and the urine had been found to contain pus. At the age of four she had had left renal colic and again pyuria had been found. After repeated renal colics, roentgenographic examination was performed at the age of six and a calculus in the left kidney was demonstrated. The attacks continued, and at the age of ten roentgenographic examination demonstrated several stones in the left kidney. Four stones were removed from the left kidney by pyelotomy and a nephrostomy was performed. In 1946 when she was eleven years old the left kidney, which was reduced to a sac of pus, was removed. Since then she felt well until 1954 when she had attacks of right lumbar pain with hematuria. Roentgenographic examination revealed a peanut size stone in the right kidney.

On admission in November, 1955, her physical

findings were essentially normal. She had no fever, the blood pressure was 140/80 mm. Hg. Urinalysis showed traces of albumin, a few leukocytes and many oxalate crystals in the sediment, a specific gravity ranging from 1.008 to 1.018, and repeated urine cultures were negative. The erythrocyte sedimentation rate was 12 mm. in one hour, the hemoglobin was 14.3 gm./100 ml., the white cell count was 6300/cu. mm. and the differential count was normal. The blood urea nitrogen was 27 mg./100 ml.; fasting blood sugar was 89 mg./100 ml.; total protein, 7.3; albumin, 4.1; and globulin, 3.2 gm./100 ml.; serum chloride, 103 mEq./L.; sodium, 130 mEq./L.; potassium, 5.6 mEq./L.; uric acid, 2.5 to 3.4 mg./100 ml.; CO₂ combining power, 26 mEq./L.; the serum calcium ranged from 9.3 to 10.1 mg./100 ml., inorganic phosphorus from 4.3 to 5.7 mg./100 ml.; the alkaline phosphatase values were 2.4, 1.8 and 4.4 Bodansky units. The urea clearance was 76 to 98 per cent of normal. A roentgenogram of the right kidney revealed a stone the size of a small nut; intravenous excretory urography revealed slight dilatation of the renal pelvis, good excretion of contrast substance, and localization of the stone in the renal pelvis. Roentgenograms of the skull, vertebra, arms, wrists, hands, pelvic bones and legs did not disclose any abnormality.

As the patient had many renal colics which prevented her from carrying on her work, and as repeated pyelograms showed that since 1954 the stone had increased in size and moderate hydronephrosis of the renal pelvis and calyces had developed, it was decided to remove the stone surgically. Right pyelotomy was performed on July 25, 1956. On operation the kidney was seen to be slightly enlarged. A stone the size of a nut was removed from the pelvis. Apart from this no other pathologic condition was found. The postoperative course was uneventful.

The patient was advised to drink 3½ L. of fluid per day during the hot summer months and 2½ L. during the cooler periods of the year. Since then she has had no lumbar pain or fever. Repeated urine examinations occasionally showed a trace of albumin, but no cells, casts or crystals.

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SPECIAL STUDIES

Aminoaciduria. Two dimensional ascending paper chromatograms of the urine were obtained on Whatman No. 1 filter paper, using the phenol solvent system of Berry et al. [3] in one dimension, and lutidine-collidine-diethylamine [4] in the other. The color was developed with 0.1 per cent ninhydrin in isopropanol [5]. The amino acid pattern of the patient's urine showed a prominent spot at the location of glycine, but was otherwise normal. (Fig. 1.) The substance responsible for this spot was verified as glycine by intensification of the spot when glycine was added to urine and by the *o*-phthalaldehyde reaction according to Curzon [6]. Acid hydrolysis of the urine did not decrease the intensity of the spot, indicating that the responsible substance was not a peptide.

A rough quantitative estimation of glycine in the urine by comparison of the chromatogram with chromatograms of glycine solutions of known concentration indicated a glycine excretion of about 650 mg. per twenty-four hours. More accurate values were obtained by microbiologic assay of glycine using a glycine- and serine-dependent *E. coli* mutant in Davis minimal medium [7]. Since the amount of serine in the patient's urine was not increased, as demonstrated in the amino acid pattern by the periodate Nessler reagent [8], daily glycine excretion was estimated by subtracting 50 mg. (average normal amount of serine excreted daily [9]) from the values obtained by the microbiologic assay. The amount of glycine excreted per twenty-four hours, estimated by this method, on six consecutive days ranged from 798 to 1,200 mg. with an average of 991 mg., as compared with the values of 113 to 218 mg. obtained in eight normal adults, average 156 mg. per twenty-four hours.

The daily total amino nitrogen excretion, determined according to King [10], was markedly elevated, ranging from 241 to 316 mg. with an average of 286 mg., as compared with the values obtained of 51 to 152 mg. in eight normal adults, average 120 mg. per twenty-four hours. The increase in urinary amino nitrogen corresponded to the excess glycine excreted.

Chromatography of serum was performed after deproteinization by addition of 9 volumes of 96 per cent alcohol; the supernatant was evaporated to dryness and the residue redissolved in distilled water to one-tenth the original volume of the serum. A chromatogram of the

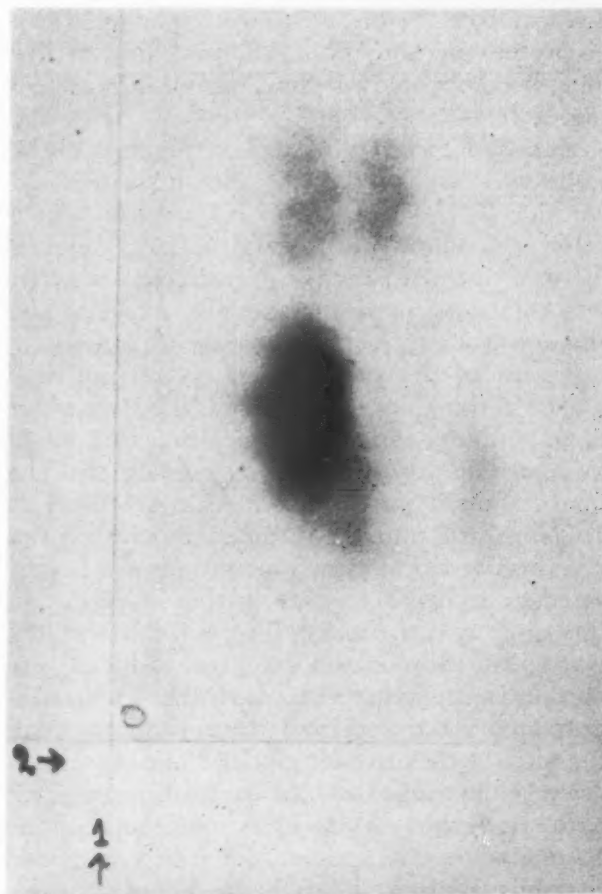


FIG. 1. Chromatogram of urine from patient S. R. The dense spot is glycine.

fasting serum showed a normal amino acid pattern with a glycine spot of normal intensity. This finding indicates that this case of glycinuria can be classified with the renal aminoacidurias.

Of interest is the excessive glycine excretion in the urine after an intravenous glycine load. An injection of 7 gm. glycine (1 gm. per 15 pounds body weight [11]) in 70 ml. saline solution was given intravenously within a period of two and a half minutes. Within the first twenty minutes 38 ml. urine containing 850 mg. of glycine (2.24 gm. per cent) were excreted; in 200 minutes a total of 1,240 mg. glycine appeared in the urine. These values may be compared with the glycine excretion in two normal subjects after an intravenous glycine load of 1 gm. per 15 pounds body weight who, within the first twenty minutes excreted 240 mg. and 285 mg., respectively (1.45 and 0.57 gm. per cent), and in 200 minutes, 394 and 340 mg. The chromatogram of the serum in the patient showed a return to normal intensity of the glycine spot after approximately two hours. The glycine excretion was not in-

fluenced by a low protein diet containing 30 gm. of protein per day; on the third day of this diet the amount of glycine excretion was 890 mg.

Analysis of Stone. Routine examination of the stone was carried out according to Winer and Mattice [12]. The stone had a reddish brown color, it was hard with a rough surface, weighed 0.7 gm. and contained 13.4 per cent water. It was composed mainly of calcium oxalate. The stone was analyzed for glycine as follows: a fragment of the stone weighing 150 mg. was soaked three times in 0.4 ml. distilled water for fifteen minutes and the three washings, obtained by centrifugation, were collected separately. The final sediment was resuspended in 0.4 ml. 1 N HCl for thirty minutes at room temperature and recentrifuged. The clear supernatant was evaporated to dryness by an air current at 60°C. and the residue was dissolved in 0.4 ml. distilled water. The solution and the three washings were chromatographed as described. The chromatograms of the second and third washings were found to be negative for glycine. The chromatogram of the acid extract of the washed fragment of the stone showed only one strong spot with the R_f of glycine. The spot was identified as glycine by addition of glycine to the extract of the stone and the *o*-phthalaldehyde reaction [6]. A rough estimation of glycine on the chromatogram by comparison with simultaneously run glycine standards gave a value for glycine of 0.5 per cent of the dry weight of the stone.

Similar analysis of eight random oxalate stones obtained from various other patients of the department of urology did not reveal glycine or other spots on the chromatograms of acid extracts of the stones. The treatment already described failed to reveal the presence of glycine in a random oxalate stone which was soaked for thirty-six hours in patient's urine containing 1 % glycine.

Investigation of Possible Metabolic Relationship between Glycine and Oxalic Acid in the Patient. The association of excessive glycinuria and oxalate and glycine in the stone prompted consideration of a possible conversion of glycine through glyoxylic acid to oxalate, which has been demonstrated to occur in the rat liver [13]. If such a metabolic pathway were present in our patient glyoxylic acid and excessive amounts of oxalic acid might be found in the urine.

However, chromatographic examination of the urine by the method of Cavallini et al.

[14,15] revealed only the usual phenylhydrazones of pyruvic and α -ketoglutaric acid, but not of glyoxylic acid. Moreover, the daily excretion of oxalic acid in the urine, determined by the method of Powers and Levatin [16] on nine consecutive days, was found to be normal (18 to 40 mg./twenty-four hours, normal up to 50 mg./twenty-four hours [17]). These results do not furnish evidence for such a metabolic relationship between glycine and oxalic acid in this case.

Studies on Calcium and Phosphorus Excretion in Urine and Intravenous Calcium Infusion Test. Calcium and phosphorus were determined by the method given in Fister's manual [18]. On a regular hospital diet containing 950 to 1,000 mg. calcium per day, the average daily calcium excretion by our patient (S. R.) amounted to 180 mg. (183,246,112), which is in the normal range [17].

An intravenous calcium infusion test was performed in order to detect osteomalacia, described in association with glycinuria by Evered [9], and to obtain evidence for hyperparathyroidism. The test was performed according to the modification by Nordin and Frazer [19] of the method described by Howard et al. [20]. Eight hours after the beginning of the intravenous infusion of calcium gluconate (15 mg. of calcium per kg. of body weight), the serum phosphorus had risen from the preinfusion value of 3.8 mg. per cent to 5.2 mg. per cent. The phosphorus excreted in the urine during the twenty-four hours from the beginning of the calcium infusion amounted to 51 mg. as compared with the twenty-four hours preinfusion value of 248 mg., i.e. a decrease of 79.4 per cent. These data are consistent with normal parathyroid function [20]. The serum calcium rose from the preinfusion value of 9.1 mg. per cent to 13.2 mg. per cent at the end of the infusion (i.e. after four hours) and returned to 10.1 mg. per cent after an additional four-hour period. The net urinary calcium output during a twelve-hour period starting with the calcium infusion, calculated according to Nordin and Frazer [19], was 43.2 per cent, which is in the normal range (27 to 55 per cent, average 41 per cent).

The phosphorus clearance determined on the third day of a diet poor in calcium and phosphorus, containing 115 mg. calcium and 250 mg. phosphorus per day, was 4.5 ml./minute. The endogenous creatinine clearance [27] was 64.5 ml./min. The phosphate/creatinine clear-

TABLE I
INVESTIGATION OF FAMILY OF PATIENT S. R.

Member of Family	Age (yr.)	History		Glycine in Urine (mg./24 hr. *)	Glycine in Serum†	Osteoporosis (X-ray)
		Renal Colic	Stones Passed or Diagnosed (including X-ray)			
Propositus, S. R.....	20	+	+	991	Normal	—
Mother, S. V.....	48	—	—	596	Normal	—
Father, S. S.....	52	—	—	195	—
Sister, D. B.....	22	+	+	632	Normal	—
Grandmother, V. R. (maternal side).....	75	+	—	593	Slight
Uncle, V. D. (maternal side).....	55	—	—	Normal†	—
Daughter of sister D. B.....	2	—	—	120

* Microbiologic assay.

† Two dimensional chromatography.

ance ratio was 0.07, which is in the normal range [22,23].

Absence of Renal Glucosuria. No glucosuria was detected on repeated random examinations, and also not after an oral glucose load, following which the blood sugar rose to 162 mg. per cent.

Estimation of Xanthine in Urine. In connection with Dent's [24] observation that glycine was liberated on hydrolysis of a xanthine stone, our patient was investigated for xanthinuria. Determination of xanthine in the urine by the xanthine oxidase method of Kalckar [25] revealed an output of 5 mg. xanthine in a twenty-four-hour sample. This value is in the normal range [24,26,27].

Investigation of Patient's Family. Chromatographic examination of the urine of members of the patient's family showed excessive glycine excretion with otherwise normal amino acid patterns in the patient's sister, mother and maternal grandmother. (Table I.) The patient's father, her maternal uncle and the two year old daughter of her sister had normal urinary glycine excretion. None of the family had glucosuria. The pedigree of this family is shown in Figure 2.

The patient did not give a family history which was suggestive of renal colic or kidney stones. A personal history was taken from the members available, their urine was examined and roentgenographic examination of the kidneys, including excretory urography, was performed. In addition, roentgenographic examination of the

skull, spine, extremities and pelvic bones was carried out in order to detect osteomalacia. (Table I.)

In the patient's twenty-two year old sister, who had glycinuria and gave a history of two right-sided renal colics during the last two years, a peanut-sized stone was detected on roentgenographic examination of the right kidney. The urinary calcium excretion on the regular hospital diet was 80 mg./twenty-four hours. Intravenous calcium infusion caused the serum phosphorus to rise from 3 mg. per cent to 5.2 mg. per cent and the twenty-four-hour urinary phosphorus output to decrease by 88 per cent; the serum calcium rose from 10.9 to 13.3 mg. per cent and the twelve hour net urinary calcium output was 34.9 per cent. The phosphorus clearance on the third day of a diet poor in calcium and phosphorus was 4.8 ml./minute. All these values are in the normal range.

The grandmother who had glycinuria had a history of renal colic but no stones had been passed and present roentgenographic examination of the kidneys was negative.

COMMENTS

In the present communication we report the occurrence of excessive urinary glycine excretion in four female members of one family, which was associated with nephrolithiasis in three of them. The one kidney stone available for examination, composed mainly of calcium oxalate, was found to contain a small amount of glycine in non-

protein or non-peptide form. It appears from the pedigree that the glycinuria is a dominant sex-limited character [28], although the pedigree is too small to be absolutely certain about this.

Glycine is a non-essential amino acid normally present in urine, the daily excretion in normal

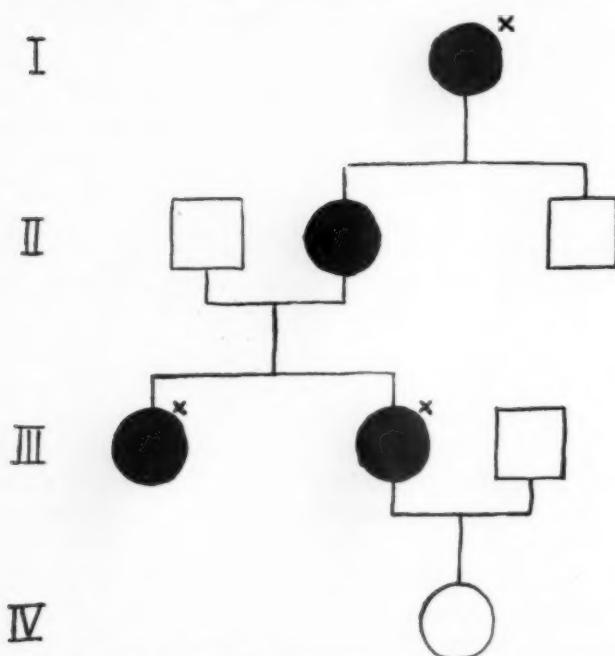


FIG. 2. Pedigree of glycinuria. Black indicates excessive glycine excretion, the asterisk nephrolithiasis.

subjects varying, according to Stein [29] from 68 to 199 mg. and as determined in the present study from 113 to 218 mg. The amounts of glycine excreted daily by the reported siblings with glycinuria ranged from 593 to 1,200 mg.

Increased glycine excretion may be caused by two mechanisms. It may be the result of an increased plasma glycine concentration—"overflow"—such as has been found in severe liver damage, in which there is generalized hyperaminoacidemia and aminoaciduria [30]. Excessive glycine excretion may also be due to a defect in tubular glycine reabsorption. The finding of a normal amino acid pattern of the serum in the presently reported subjects with excessive urinary glycine excretion indicates that this glycinuria can be classified with the renal aminoacidurias, in which there is a disturbance in tubular amino acid reabsorption.

The degree of disturbance in tubular glycine reabsorption in patient R. S. may be estimated from the glycine:creatinine clearance ratio. Taking the patient's plasma glycine level as 1.5 mg. per 100 ml. (estimated from the serum

chromatogram) and using the average daily plasma glycine clearance was calculated as 46 ml. per minute. Consequently, the glycine:creatinine clearance ratio was $\frac{46}{64.5} = 0.71$; or, about

70 per cent of the glycine filtered in the glomeruli was excreted in the urine. This may be compared with a normal excretion of only 7 per cent of filtered glycine, calculated from a normal daily glycine excretion of 156 mg., a normal plasma glycine level of 1.5 mg. per 100 ml., and a normal endogenous creatinine clearance of 95 ml. per minute [27].

Increased glycine excretion due to renal disturbance is a common feature of those syndromes in which there is gross aminoaciduria with abnormal amino acid excretion pattern, such as the De Toni-Fanconi syndrome [4,9], Wilson's disease [37] and H syndrome [32]. In some of these instances of gross aminoaciduria, glycine excretion is only moderately increased as compared with several other amino acids, as is the case in H syndrome [32]. In others the most striking increase of amino acid excretion is in glycine, as in certain cases of osteomalacia described by Anderson et al. [33]. In some of these syndromes there are additional tubular reabsorption defects of glucose and phosphate, as in the De Toni-Fanconi syndrome [34].

Only a few renal aminoacidurias have been described in which excessive glycine excretion was the main abnormality and associated with increased excretion of only a small number of other amino acids. Clarkson [35] reported aminoaciduria occurring in exposure to mercury vapor, in which glycine and alanine made up 80 per cent of the total urinary amino acids. Evered [9] mentioned unpublished observations of Astrup and Dent on patients with vitamin D-resistant rickets or osteomalacia, who exhibited a high glycine excretion and in addition excreted increased amounts of proline and L-methylhistidine.

The renal aminoaciduria described in the present communication is different from that reported by Evered, in that the glycinuria is not accompanied by increased excretion of other amino acids, judging from the data obtained by two dimensional paper chromatography. There are additional arguments indicating that we are dealing here with a syndrome different from that which was described by Evered. His patients, one female and one male, both short in stature, had gross osteomalacia on roentgenographic examination, and phosphaturia with a low renal

threshold for phosphate; the female patient had a low serum phosphate level, while in the male, who was examined after vitamin D₂ therapy, the serum phosphate level was normal. In contrast, none of our cases with glycinuria had gross osteomalacia, and in those examined (the patient, S. R., and her sister, D. B.) the serum phosphate level was normal, there was no hyperphosphaturia and the intravenous calcium infusion test [19] gave normal results. Furthermore, the association of the glycinuria with nephrolithiasis is not mentioned in Evered's cases.

Evered [9] mentions the possibility that in patients with osteomalacia the association of phosphaturia and glycinuria is related to competition of phosphate and glycine for reabsorption from the kidney tubule (Ayer et al. [36]) and that the increased urinary glycine, associated with increased proline excretion, is connected with the high glycine and proline content in the collagen of the organic matrix of the bone. However, our patients, who had a much higher urinary glycine excretion than Evered's, did not show osteomalacia, hypophosphatemia, hyperphosphaturia or prolinuria. This would seem to deny that such relationships of glycine and phosphorus excretion, and of glycine loss and disturbance in organic bone matrix, are obligatory. It is probable that in Evered's osteomalacic glycinuric patients the low renal threshold for glycine and also for phosphorus reflects independent renal tubular defects, the osteomalacia being related to the mineral loss.

The mechanism of tubular glycine reabsorption is not well known. Pitts [37] proposed a common mechanism for renal tubular reabsorption for glycine, alanine, glutamic acid and arginine in the dog, the amino acids being bound within the cells of the proximal convoluted tubules by one and the same hypothetical substance. However, according to the experiments of Beyer et al. [38], renal tubular glycine transport in the dog may be regulated by a separate mechanism, which is different from that for other amino acids. The occurrence of isolated excessive glycine excretion in our patients indicates the unique specificity of the tubular absorption mechanism for this amino acid in man. Our observations show that this mechanism of glycine absorption is not necessarily related to that active in tubular glucose and phosphate absorption.

That nephrolithiasis may be linked in some way to the aminoaciduria is indicated by the

demonstration of kidney stones in the two sisters (S. R. and B. D.) and the history of renal colic in the grandmother. Analysis of one available stone demonstrated the presence of a small amount of glycine in addition to a large amount of oxalate. The exact form in which glycine was present in the stone has not been determined. The amino acid could not be washed out by water but was extracted by treatment of the stone with 1 N HCl for thirty minutes at room temperature. Glycine is generally present in renal stones as a part of the protein or peptide portion of the molecules of the organic matrix (Boyce [39]), as shown by chromatographic analysis of stone matrix hydrolyzed with 6 N HCl for twenty hours in a sealed tube at 100°C. Glycine may also be obtained by hydrolysis of xanthine stones [24]. The mild conditions under which the glycine could be extracted from the stone obtained from our patient S. R. indicate that it was present in non-protein or non-peptide form. Furthermore our patient had no xanthinuria. The observation that the glycine was released only after extraction with dilute hydrochloric acid indicates that the glycine was either absorbed to one of the constituents of the stone or present in a chemical form from which glycine was released by this treatment. That this is a special feature of this specific stone is shown by the failure to obtain glycine by acid extraction at room temperature from ten random oxalate stones which were obtained from patients suffering from nephrolithiasis.

The cause and significance of the presence of glycine in the oxalate stone are not understood. It is possible that the amino acid was secondarily included in the stone which bathed in urine of excessively high glycine concentration. An attempt to obtain glycine by similar treatment of a random oxalate stone, soaked for thirty-six hours in the urine of patient S. R. with excessive glycine excretion, was negative.

Whether or not the increased glycine concentration of the urine played a role in the formation of the oxalate stone is not known. A metabolic pathway from glycine via glyoxylic acid to oxalic acid has been demonstrated in rat liver homogenates by Weinhouse [13]. The possibility was considered that oxalic acid was formed from glycine; for instance, in the renal tubular cells or by bacteria in the urinary tract. However, no evidence for such a mechanism was found in our patient, as oxalic excretion was not increased and no glyoxylic acid was demonstrated in the

urine. It would be of great interest to analyze the stone of the patient's sister (B. D.) for the presence of glycine; however, this must wait until she passes the stone or an indication for surgical intervention supervenes.

The association of this hereditary aminoaciduria with nephrolithiasis prompts a comparison with cystinuria, hitherto the only other known aminoaciduria associated with nephrolithiasis. Many differences stand out however. Cystinuria is not infrequent [40], while hereditary glycinuria must be very rare, considering the fact that glycinuria as a single hereditary aminoaciduria has not been previously reported, although chromatographic urine examinations are widely performed. While cystinuria in most cases is inherited through a recessive gene [41], the glycinuria described here apparently has a dominant pattern of inheritance. Furthermore, while urinary calculi in cystinuric patients are composed mainly or exclusively of cystine [42], in the present case of glycinuria the stone was composed mainly of oxalate and its glycine content was very small. Finally, the mechanism responsible for the presence of non-protein glycine in the stone must be completely different from that acting in cystine stone formation. While cystine stone formation is due to precipitation of cystine from supersaturated urine [43], the urinary glycine concentration in the glycinuric patient remained far below the saturation level of this amino acid.

SUMMARY

Excessive urinary glycine excretion was found in four members of a family and was associated in three members with nephrolithiasis.

The glycinuria was due to a renal mechanism. Failure to reabsorb glycine was not associated with defective reabsorption of other amino acids or of phosphate or glucose.

A kidney stone obtained from one of these patients was composed mainly of calcium oxalate and contained a small amount of glycine present in non-protein, non-peptide form.

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Renal Clearance of Lysine in Cystinuria*

Pathogenesis and Management of This Abnormality

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IN the past decade three groups of investigators employing the analytic methods of microbiologic assay [1], column [2] and paper [3] chromatography have demonstrated that the urine of subjects with cystinuria contains excessive amounts of three other amino acids in addition to cystine, namely, lysine, arginine and ornithine. Genetic evidence accumulated by Harris and Warren [4] indicates that cystinuria may be inherited in either an homozygous or heterozygous form. In the latter event, smaller amounts of the amino acids are excreted but the quantity of cystine is usually large enough to give a positive nitroprusside test and perhaps to explain the high incidence of cystinuria of approximately 1 per 500 healthy young adults reported by Lewis [5]. The limited solubility of cystine is a factor in the only important complication that has been recognized, cystine calculi. Fortunately renal calculi do not develop in all afflicted individuals. The calculi are usually unilateral but may be bilateral and in either event are particularly prone to recurrence.

Dent and his colleagues, who have contributed a great deal to the knowledge of this subject, have recently presented evidence that the defect in cystinuria is not in the nature of a generalized disturbance of amino-acid metabolism but rather one of impaired renal tubular reabsorption of these particular amino acids [6]. Utilizing polarographic analysis as a means of measuring plasma and urinary cystine, Dent et al. [7] made the interesting observation that the clearances of cystine and inulin, determined simultaneously, were identical. Since, in cystinuria, the essential amino acid, lysine, is usually excreted in larger amounts than cystine, studies were undertaken to

determine the extent of the tubular reabsorptive defect relevant to lysine. In addition, certain other studies on the excretion of glycocholate and the effect of diet on the excretion of cystine, lysine and arginine have been performed. The results obtained in these and earlier studies of the renal clearances of individual amino acids in normal subjects [8,9] as well as the observations made by others in various aminoacidurias, provide the basis for the discussion which follows.

METHODS

The plasma and urinary concentrations of the individual amino acids were determined microbiologically [10]. This method gives values for the twenty-four-hour excretion of lysine by normal subjects which tend to be somewhat lower but in the same general range as those values reported by Stein who utilized the method of column chromatography [11]. In thirty-five normal subjects the plasma concentration of lysine was determined to be 3.2 ± 0.64 mg. per 100 ml. This value, on a basis of a multiple comparison procedure [12], is not significantly different from those reported by other investigators who employed different methods of analysis or deproteinization [13-17].

Deproteinization was accomplished with heat and acetic acid or by ultrafiltration. Separate studies have revealed no significant difference in the values for lysine obtained on the same plasma specimen deproteinized by these two methods, although the ultrafiltrate values tend to be slightly lower. With other individual amino acids, notably cystine, recoveries from plasma are satisfactory but the heat-acetic acid filtrates give fasting values which are significantly higher than those obtained with other methods of deproteinization. These observations have raised the problem of protein-binding as well as that of the best means of deproteinization for analysis of individual amino acids; these matters, therefore, are being

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further investigated. Stein and Moore and Dunn et al. have recently commented on the problem of deproteinization [13,18]. For these reasons and because of the improbability of renal synthesis of an essential amino acid, only the clearance data on lysine are presented at this time.

Seven studies were performed in four patients in whom the diagnosis of cystinuria was clearly established: D. G. (age, forty-four years; height, 157.5 cm.; weight, 88.6 kg.); N. F. (age, twenty-two years; height, 168.9 cm.; weight, 65.9 kg.); W. F. (age, thirty-seven years; height, 174.0 cm.; weight 54.1 kg.); and R. P. (age, twenty-five years; height, 172.7 cm.; weight, 61.1 kg.). The only female subject, D. G., had a calculus in the right kidney. No radiographic evidence of calculi was obtained in the other subjects at the time these studies were performed although all had had proved cystine stones at some time in the past.

The glomerular filtration rate (GFR) was measured by means of inulin clearance as previously described [8]. In one of the studies on subject D. G., after three control periods a ten per cent solution of free amino acids was infused at 3.4 ml. per minute and three additional collection periods were obtained. In subject N. F. a similar test was performed substituting a 1.0 per cent solution of L-lysine for the amino acid solution. The lysine was administered at a rate of 6.0 ml. per minute. Initially, 100 ml. of the solution being studied was administered and twenty minutes were allowed for equilibration. The exact composition of the 10 per cent solution of amino acids (lot B-27)* has been reported [8]. The statistical analyses of the data were made by means of standard *t*-test techniques [19].

In three patients with cystinuria and in six normal subjects, three females and three males, the excretion of glycocyamine was measured. The subjects drank 200 ml. of water hourly and an accurately timed six-hour specimen of urine was collected. On the following day the subjects drank a glass of tomato juice to which had been added 7.0 gm. of arginine hydrochloride, and a glass of grape juice containing an equimolar amount (2.5 gm.) of glycine. The same experimental protocol was then followed as on the previous day. In this way each individual served as his own control. The diet ingested was the same on both days during the test period. After removal of the arginine by permutit [20], the glycocyamine was measured colorimetrically by the method of Sims [27].

RESULTS

Plasma Concentration of Lysine and Glomerular Filtration Rate in Cystinuria. The average of seven determinations of the fasting plasma lysine concentration in the four subjects was 2.4 ± 0.56 mg. per 100 ml. compared with the normal value of 3.2 ± 0.64 mg. per 100 ml. This suggests

* The amino acids solution used in these studies was generously provided by Merck & Company, Inc.

that the plasma concentration of lysine is lower in patients with cystinuria than in normal subjects but the studies will have to be extended to prove significance at an acceptable level of confidence. Dent and his associates have demonstrated that the plasma concentration of cystine

TABLE I
GLOMERULAR FILTRATION RATE IN PATIENTS WITH
CYSTINURIA

Subject	Period						Surface Area M ²
	Control			Load			
	1	2	3	4	5	6	
D. G.	78	75	70	87	75	68	1.89
	...	84	76
N. F.	106	106	104	102	96	86	1.75
	...	114	115
W. F.	106	103	104	1.65
	...	96	66*
R. P.	126	127	124	1.73

NOTE: All measurements in control and load periods in ml./min.

* Incomplete urine collection.

TABLE II
ENDOGENOUS CLEARANCE AND PER CENT REABSORPTION OF
LYSINE IN SUBJECTS WITH CYSTINURIA

Subject	Clearance (ml./min.)	Reabsorbed (%)
D. G.	41.8	43.3
D. G.	57.2	28.5
N. F.	48.8	53.6
N. F.	53.7	53.0
W. F.	44.6	53.5
W. F.	68.8	34.4
R. P.	79.0	37.0

is lower in patients with cystinuria than in normal subjects [7].

When the values for glomerular filtration rate, listed in Table I, are corrected for surface area, it will be seen that the GFR was normal in subjects R. F. and N. F., slightly reduced in W. F. and definitely reduced in D. G. This latter patient (D. G.) also had a proportionately reduced renal plasma flow. These results are such as one might anticipate, namely, that cystinuria, *per se*,

TABLE III
PLASMA CONCENTRATION, FILTERED LOAD AND EXCRETION VALUES OF INDIVIDUAL AMINO ACIDS DURING
EXPERIMENTS IN SUBJECTS D. G. AND N. F.

Subject and Amino Acids	Plasma Concentration*					Filtered Load†				Excretion†			
	Fast- ing‡	Period after Loading§				Fast- ing‡	Period after Loading			Fast- ing‡	Period after Loading		
		1	2	3			1	2	3		1	2	3
Subject D. G.:	(74.3)	(87.7)	(74.9)	(67.6)
L-alanine.....	4.8	5.3	5.6	5.8	6.6	3.63	4.68	4.27	4.12	nil	0.26	0.07	0.07
L-glutamine....	9.0	10.7	10.6	10.2	9.8	6.59	9.28	7.86	6.83	0.13	0.42	0.31	0.31
Glycine.....	1.9	15.2	14.2	15.6	16.0	1.45	12.7	11.0	10.6	0.24	7.1	5.4	5.1
L-histidine....	1.7	4.8	4.8	4.9	5.4	1.29	4.16	3.66	3.43	0.11	1.27	1.10	1.02
L-isoleucine....	1.5	7.6	8.0	8.6	9.2	1.12	6.72	6.14	5.95	0.02	0.10	0.09	0.06
L-leucine.....	2.1	9.8	12.0	12.7	14.2	1.53	9.10	9.21	8.92	nil	0.08	0.07	0.06
L-lysine.....	2.6	8.0	8.5	9.6	9.3	1.95	7.1	6.7	6.4	1.1	8.3	6.8	5.7
L-methionine...	0.4	3.7	4.1	4.6	4.8	0.3	3.32	3.20	3.16	nil	0.14	0.11	0.09
L-phenyl- alanine.....	0.98	3.6	4.0	5.0	5.2	0.73	3.19	3.22	3.43	0.01	0.09	0.09	0.07
L-proline.....	1.3	3.2	3.5	3.6	3.7	1.0	2.86	2.66	2.47	nil	0.13	0.11	0.10
L-serine.....	1.8	3.5	3.2	3.7	3.6	1.34	2.95	2.54	2.49	0.02	0.46	0.35	0.32
L-threonine....	3.9	7.2	6.9	7.5	8.5	2.92	6.16	5.32	5.31	0.05	0.77	0.72	0.67
L-tryptophan...	0.9	2.0	2.1	2.0	2.4	0.69	1.78	1.51	1.43	0.01	0.05	0.05	0.04
L-tyrosine....	1.3	1.7	1.8	2.0	2.0	0.95	1.50	1.42	1.35	0.01	0.03	0.03	0.02
L-valine.....	3.0	9.0	9.1	9.3	10.5	2.24	7.83	6.88	6.56	nil	0.09	0.07	0.06
Subject N. F.:	(105)	(102)	(96)	(86)
L-lysine.....	2.5	11.0	10.9	12.5	13.4	2.65	11.2	11.1	11.1	1.22	10.8	11.2	9.3

NOTE: Figures in parentheses represent glomerular filtration rates.

* Measurements are in mg./100 ml.

† Measurements are in mg./min.

‡ Fasting values are means of three collection periods.

§ Plasma amino acid concentrations were determined at the beginning and end of each period.

has no effect on renal hemodynamics, any changes therein being secondary to the complications of calculi and infection.

Endogenous Tubular Reabsorption of Lysine and Response to Load. In normal subjects the endogenous clearance of lysine is less than 1.0 ml. per minute and the tubular reabsorption is virtually complete (>99 per cent) in the fasting state [8], whereas in patients with cystinuria the endogenous clearance approximates 55 ml. per minute and the per cent of reabsorption is in the order of 45. (Table II.)

Although the actual concentrations measured are low, the calculated amount reabsorbed is significantly different from zero ($p \leq .05$). The true magnitude of the reabsorption is subject to some question, however, because the concentrations approach the limits of sensitivity of the

analytical methods employed. The mean value for the ratio of clearance lysine/clearance inulin is 0.56 with a range of 0.47 to 0.71. Since the ratio does not approximate unity in any of the experiments, the results are interpreted as indicating that some reabsorption of lysine does occur, probably in the order of 1.0 mg. per minute.

The results obtained in the loading studies performed on subjects D. G. and N. F. are presented in Table III. The tubular reabsorption of alanine, glutamine, glycine, histidine, isoleucine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine is normal both in the fasting state and under load. When the plasma concentration of lysine was increased, no significant quantity of the added amount filtered was reabsorbed and

the values obtained for the ratio of clearance lysine/clearance inulin are 1.02 (D. G.) and 0.92 (N. F.).* The clearance of lysine under load, therefore, approaches the inulin clearance.

Excretion of Glycocyamine. Both the normal subjects and the patients with cystinuria showed

TABLE IV
EXCRETION OF GLYCOCYAMINE BEFORE AND AFTER
ADMINISTRATION OF ARGININE AND GLYCINE IN
NORMAL SUBJECTS AND IN SUBJECTS WITH
CYSTINURIA

Subjects	Control (mg./6 hr.)	Load Arginine and Glycine (mg./6 hr.)
<i>Normal Subjects</i>		
C. W.	40.2	84.5
E. M.	26.8	72.8
P. D.	22.0	42.0
M. D.	16.0	56.6
V. G.	36.6	78.2
E. S.	77.1	112.0
<i>Subjects with Cystinuria</i>		
W. F.	68.0	130.0
J. T.	51.0	95.3
D. G.	49.0	62.8

an increase in glycocyamine excretion after the administration of equimolar amounts of arginine and glycine. (Table iv.) The somewhat smaller response made by subject D. G. may have been due to the reduced renal plasma flow.

COMMENTS

Conditions Associated with Aminoaciduria. Aminoaciduria has been reported in association with the De Toni-Fanconi syndrome [22-24], Lowe syndrome [25,26], kidney disease [27-29], Wilson's disease [30,31], liver disease [32,33], H. disease [34], rickets [35], galactosemia [36,37], ascorbic acid deficiency [38], lead and "Lysol" poisonings [39,40], postoperatively [41], in burns [42,43] and in patients with progressive muscular dystrophy [44]. It has been produced in experimental animals by maleic acid [45], uranium poisoning [46] and vitamin E deprivation [47]. One may continue to anticipate, until more precise information on the factors governing

* The value for the GFR (86) in the third period under load in N. F. is undoubtedly low. If this period is omitted the ratio $\frac{\text{clearance lysine}}{\text{clearance inulin}} = 0.97$.

normal amino-acid transport is available, that postulations as to common denominators underlying the aminoacidurias and other abnormalities encountered in this panorama of pathology will remain purely speculative. It is instructive, however, to comment at this time on certain observations and on some of the experimental data which have been collected and which are especially relevant to the aminoaciduria of cystinuria but of indirect or inferential significance in other aminoacidurias.

Individuating Features of Cystinuria. Among the aminoacidurias, cystinuria has certain individuating features. Only four amino acids—cystine, lysine, arginine and ornithine—are excreted in excessive amounts. The mechanism responsible for the increased excretion is different from that encountered in either the histidinuria of pregnancy, which is due primarily to an increase in glomerular filtration rate [48], or that of phenylketonuria [49], which is, in a sense, another "overflow" aminoaciduria due to the high plasma levels resulting from the inability to convert phenylalanine to tyrosine. The quantities excreted in cystinuria are much greater than those reported in other aminoacidurias [23,26,27,30,31,38,41,42]. The magnitude of the losses are such that they obviously cannot be explained on a basis of a population defect relegated to a small number of inactive nephrons such as has been postulated in the Fanconi syndrome [28]. Despite the gravity of the losses of these amino acids, one of which is essential and all of which are important in normal metabolism, the patient with cystinuria suffers no serious or readily apparent nutritional consequence.* Finally, and of considerable importance, is the finding that on loading with lysine no significant additional amount is reabsorbed. In preliminary studies with arginine, similar results have been obtained [52].† These

* Despite the fact that the average American diet provides these amino acids in amounts sufficient to cover the urinary losses and requirements for nitrogen equilibrium [50,51], the absence of apparent nutritional complications remains somewhat surprising in view of the rapid and large diversion of these amino acids into the urine. Cystinuria suggests itself as an interesting condition in which to study protein and amino-acid metabolism, particularly during periods of protein deprivation.

† On the basis of these studies of arginine clearance and the measurements that have been made of the amounts excreted, it seems justifiable to consider the tubular transport defect relevant to arginine as quantitatively similar to that of cystine and lysine. There is very little information available on ornithine reabsorption.

TABLE V
EXCRETION OF CYSTINE, ARGININE, LYSINE AND ORNITHINE IN NORMAL SUBJECTS AND IN SUBJECTS WITH CYSTINURIA

Amino Acid	Normal Subjects			Subjects with Cystinuria			
	Harper et al. [53]	Stein [77]	Hier [54]	Authors	Stein [2]	Dent et al. [7]	
	Mean	Mean	Mean	Mean S.D.*	Mean S.D.	Mean S.D.	
Cystine.....	0.055	0.010	0.088	1.21 ± 0.41	0.73 ± 0.24	0.86 ± 0.27	
Arginine.....	0.013	0.010	0.021	1.15 ± 0.26	0.83 ± 0.30	
Lysine.....	0.011	0.019	0.034	1.94 ± 0.72	1.80 ± 0.59	
Ornithine.....	nil	0.38 ± 0.14	

NOTE: All measurements in gm./24 hours.

* S.D. = standard deviation.

observations are in sharp contrast to those which have been made in the aminoaciduria of nephrosis [27], chronic renal disease [28], Wilson's disease [30], De Toni-Fanconi [26,28] and the Lowe syndromes [26]. In those conditions, as the filtered load is increased both the amounts of amino acids reabsorbed and excreted are increased, and in this respect the tubular response is not qualitatively different from that observed in normal human subjects [8,9].

Tubular Reabsorption of Cystine, Lysine and Arginine in Cystinuria. The quantities of the individual amino acids excreted in cystinuria are presented in Table v. It is not possible to compare the values found by the individual investigators because of variations in renal function among the patients studied and the different analytical methods employed. From these measurements of the amounts excreted (Table v), a knowledge of the plasma concentration of these amino acids, and the results of the clearance studies performed with lysine and cystine, it appears to be clearly established that the tubular reabsorption of the involved amino acids in cystinuria is either minimal or, for practical purposes, non-existent. The limitations in the precision of available analytical methods, as well as in that of measuring glomerular filtration rate, are such as to prevent one from being more specific.

An Explanation for the Tubular Defect. An explanation for this finding may be that in the homozygous form of cystinuria the tubular transport system or systems are present in only

trace amounts while in the heterozygous form it or they are present in less than normal amounts. The transport mechanism in the former case is slow and easily saturated and its limited capacity is exceeded even in the fasting state. The transport system may be of the membrane carrier type wherein entrance into the cell is contingent upon the formation of a complex [55]; and since the carrier component is deficient, the low penetrability of the actively reabsorbed amino acids is evidenced in their increased excretion. Any reabsorption of lysine in cystinuria is accomplished by an active process; diffusion plays no role of significance since loading disclosed no detectable change in the amount reabsorbed. The L-forms of amino acids are normally reabsorbed by a system of active or uphill transport; whether or not there is any component of passive diffusion has not been evaluated. Since substances which are actively transported frequently have a low or minimal cellular penetrability [55], the results obtained with lysine-loading in cystinuria would indicate that reabsorption of the L-forms is exclusively active. This is an extremely interesting observation since the transport systems for cells of other tissues include a component of diffusion [56]. Further studies by Christensen and Riggs indicate that the manner in which amino acids chelate is closely connected with the manner in which they are transported [57]. A variation, therefore, of what might be essentially the same hypothesis is the suggestion that the involved amino acids are not reabsorbed in significant

amounts because normally they are chelated in some special way and in cystinuria this step cannot be performed.

Normally, the tubular reabsorption of the D-isomers of alanine and methionine is less complete than that of the L-forms and these findings have been interpreted as indicating that the D-forms are reabsorbed by a process of passive diffusion [8,58]. In analyzing the data published in one of these investigations [58] the effect of urine flow cannot be evaluated but it can be shown that with increasing filtered loads the per cent reabsorption decreased strikingly. This is not consistent with an exclusively passive diffusion process and the data can as well be interpreted as indicating that the D-forms have a weaker affinity for the transport mechanism. Clearance studies are not the ideal experimental system for investigating diffusion, for only that which goes in and comes out of the tubule is measured, and the point at issue is what goes through when the concentrations on either side of the membrane are altered. The problem of analytical accuracy in available methods of measuring the D-isomers is an additional difficulty in studying this specific matter. If passive diffusion has a significant role in reabsorption, one might speculate that in cystinuria the D-forms would be reabsorbed to a greater extent than the L-isomers. Unless the two isomers are reabsorbed by entirely different mechanisms, which is unlikely, it is improbable that any D-lysine would be reabsorbed on loading, for none of the L-form was reabsorbed under these circumstances and passive diffusion is independent of stereoisomerism. The findings of Dent and others, that the tubule in cystinuria is unable to reabsorb cystine in either isomeric form, is compatible with this reasoning [7].

During loading with a mixture of amino acids in normal subjects the excretion of cystine is increased in the absence of any significant change in filtered load [8,9]. This is interpreted as an example of competition for reabsorption but whether other amino acids or metabolites are the successful competitors has not been determined. Another possible explanation, therefore, for the findings in cystinuria is that normally the reabsorptive system is shared by the involved and non-involved amino acids or their metabolites; and these latter substances, for one reason or another, have a greater affinity for the system in cystinuria—thus blocking the reabsorption of the involved amino acids. Al-

though this may be a factor in the case of cystine, it appears less likely to be an important factor in the case of lysine or arginine, for in normal subjects the reabsorption of these amino acids remains quite complete even in the presence of a very high filtered load of a mixture of amino acids [9]. On this basis alone one would expect increased excretion of other amino acids if impairment of a shared mechanism were an important factor in cystinuria.

One possible additional explanation for the findings in cystinuria which should be mentioned is that the involved amino acids are complexed or modified in such a way as to render the tubular cells impermeable. Brand et al. suggested, on a basis of some observations made with the Sullivan reaction and the partitioning of sulfur in the urine of patients with cystinuria, that cystine was excreted as a complex which was thought to be a peptide or simple protein [59]. Strong evidence against this particular possibility is the absence of any significant change in the quantities of cystine, lysine and arginine in the urine of cystinuric subjects after hydrolysis [1,2]. One might speculate, however, that the complexing is with some unknown or as yet unidentified substance. Although there is no direct evidence to the contrary, this seems unlikely; for the x-substance would have to be absent in normal subjects and present in virtually unlimited amounts in the patient with cystinuria in order to prevent, as it does, any significant reabsorption of lysine on loading. Also, in predicating this x-material the question arises as to whether the defect in cystinuria is in the filtrate or in the tubules.

Tubular Metabolism and Glycocyamine Excretion; Implications. Another observation made in the present studies which is worthy of comment is the finding of an increased excretion of glycocyamine following the administration of glycine and arginine to patients with cystinuria. (Table IV.) Borsook and associates have shown that the kidney performs the transamidation reaction whereby glycocyamine is synthesized from arginine and glycine [60,61]. The reaction was not observed to take place in any other organ or tissue in any of the animals studied. If one grants that this reaction takes place in the tubular cells and that the luminal surface of these cells is virtually impermeable to arginine in cystinuria, then the implication to be drawn from these results is that other sources of guanidyl groups are available for the reaction or that the trans-

port mechanism for arginine is different on the vascular and luminal surfaces of the cell.

Considerations in Management and Treatment. In the light of this recent information concerning the pathogenesis of cystinuria a few comments on the complication of renal calculi are relevant. An

returned toward those of the control specimen on the high protein diet. The decrease in cystine excretion which can be achieved by dietary restriction and a knowledge of the relatively minute amounts of methionine (1.0 to 2.0 gm.) normally needed to maintain nitrogen balance

TABLE VI
EFFECT OF DIET AND A METHYL DONOR ON EXCRETION OF AMINO ACIDS IN SUBJECT (N. F.) WITH CYSTINURIA

Day	Diet	Arginine	Cystine	Lysine
0	Usual	1.17	1.30	3.24
3	Rice alone	0.53	0.87	1.31
3	Rice and betaine	0.60	0.92	1.55
5	High protein	1.50	2.11

NOTE: All measurements in gm./24 hours.

important but not the sole factor in the development of renal calculi is the insolubility of cystine and prime desiderata in management, therefore, are to decrease cystine excretion or to render it less likely to precipitate. Decreasing excretion could, in theory, be accomplished by increasing its tubular reabsorption or by decreasing the dietary intake. It would seem quite unlikely that reabsorption could be increased over a transport system which is congenitally absent or present in only trace amounts and attempts aimed at the specific tubular defect appear, therefore, to hold little promise of success. One may predict, on the other hand, that dietary restriction will decrease excretion to a minimal level for, in the absence of any significant tubular reabsorption, cystine excretion is a function of plasma level. Since the urinary cystine is derived primarily from methionine, the supplementation of a diet low in methionine with a methyl donor such as betaine might further decrease the cystine excretion by decreasing the conversion of methionine to homocysteine. In Table VI the results of some dietary studies are presented. The patient, after collecting a control urine, was given a rice diet for six days, on the last three days of which he ingested 20 gm. of betaine daily. On the third and sixth day the urine was collected and the amino acids measured. Following this he was given a diet containing 150 gm. of protein, for five days, and urine was collected on the fifth day. It will be noted that the excretion of all three amino acids decreased on the low protein diet and that the values for cystine and lysine

TABLE VII
SOLUBILITY OF CYSTINE IN WATER AND IN URINE WITH AND WITHOUT ADDED LYSINE PLUS ARGININE (ROOM TEMPERATURE)

	Cystine Solubility	
	Control	Lysine plus Arginine
Water.....	8.7	12.0
Urine.....	22.6	22.6

NOTE: All measurements in mg./100 ml.

[62] are facts which should not be neglected in therapy, particularly in those patients with compensated renal function. In the present study the administration of betaine was of no additional advantage in decreasing cystine excretion. Others using choline as the methyl donor have had a similar experience [63,64].

The prime intention of current therapy is to minimize the opportunity for cystine precipitation by "round the clock" alkalinization and maintenance of a dilute urine. Due attention should always be given to the possibility of infection, particularly with urea-splitting organisms. The solution suggested by Eisenberg et al. appears to be a satisfactory and well tolerated form of alkali therapy [65]. It is interesting to note that the solubility of cystine in normal urine is greater than in water and that the addition of lysine and arginine to the water solution increases cystine solubility but has no apparent effect on the solubility in urine. (Table VII.) It would appear that factors other than mutual amino-acid solubility are the more important determinants of cystine solubility in urine. Measures directed at rendering the physicochemical environment less conducive to precipitation by altering the protective colloidal content of the urine or by prevention of nidus formation deserve further investigation.

SUMMARY

Cystinuria is an inherited abnormality in which unusually large amounts of cystine, lysine,

arginine and ornithine are excreted in the urine.

Simultaneous measurements of the inulin and lysine clearances indicate that in the fasting state a very small amount of lysine is reabsorbed from the glomerular filtrate. The renal tubules are unable to reabsorb any additional amount and, on loading with lysine, their clearance value approaches that of inulin. A suggested explanation for this tubular defect is that in the homozygous form of cystinuria the transport system is present in only trace amounts. The transport system may be of the membrane carrier type and its limited capacity is exceeded even in the fasting state. Any reabsorption which does occur is accomplished by an active mechanism and passive diffusion plays no role of significance.

Patients with cystinuria respond normally to the administration of glycine and arginine in that the excretion of glycocholate is increased.

Therapeutic efforts directed at the specific tubular defect appear to hold little promise. The decrease in cystine excretion which can be accomplished by dietary restriction should not be neglected. The addition of a methyl donor to a restricted dietary intake offers no additional advantage. Measures directed at rendering the physicochemical environment less conducive to precipitation deserve further study.

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Marfan's Syndrome*

A Report of Three Patients with Aneurysm of the Aorta

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THIS syndrome was first reported by Marfan [1], in 1896, as "pied d'aragne" (spider feet) and now bears his name. In 1902 Achard [2], because of the spider-like appearance of the extended fingers, called it arachnodactyly. He also was the first to report the familial occurrence of this disease. Since that time over 350 cases have been reported, particularly in the French and German literature.

Piper and Irvine-Jones [3] first brought this syndrome with its frequently associated congenital malformations of the heart to the American literature. Bear, Taussig and Oppenheimer [4], in 1943, described aneurysmal dilatation of the aorta in two adults. Rados [5] reviewed the literature through 1939 and published a comprehensive report on 211 cases in 1942, describing ten patients with eye involvement, mainly ectopia lentis. This was first included in the syndrome by Boerger [11].

The syndrome is characterized clinically by an abnormal lengthening and thinning of the fingers and toes, as well as of the long bones, a prominent long palate, relaxation of the ligaments, loss of subcutaneous fat, poorly developed hypotonic musculature, asthenic body build, a dolichocephalic head with old-appearing features, kyphosis, funnel shaped chest, and subluxation of the lens of the eye. Forty-six per cent of patients with this syndrome have cardiac abnormalities such as a septal defect, valvular lesions or aneurysm of the aorta. These cardiac lesions may simulate rheumatic heart disease, or rheumatic valvular lesions may be superimposed. Pulmonary anomalies (abnormal lobation, congenital cystic disease) are frequent [10]. Some patients do not show the typical picture of the syndrome, and a forme fruste may be present. The familial incidence of the disease is well known.

Lutman and Neel [6] reported that in a kinship of forty persons seventeen members probably had Marfan's syndrome, but that there was great variability in expression of the syndrome in the various members of the family. Black and Landay [7] reported Marfan's syndrome in a mother and four children.

The following three patients with aneurysmal dilatation of the ascending limb of the aorta emphasize the fact that this finding, as well as dissecting aneurysm of the aorta, is a serious complication of Marfan's syndrome. It frequently causes death in the adult patient by producing marked aortic insufficiency and congestive heart failure.

CASE 1. This thirty-two year old white man (J. A.) was admitted to the hospital on April 28, 1955, with symptoms of congestive heart failure (shortness of breath, basal rales, hepatomegaly, peripheral edema and diastolic gallop rhythm). The patient had been in apparent good health until 1941 but since then gave a history of palpitation and cold sweats. A cardiac murmur was first discovered three years before this admission. In October, 1954, a cough developed, which was productive of small amounts of yellow-green sputum, and on one occasion he had a minimal amount of hemoptysis. Two weeks prior to admission he noted increased cough, nocturnal dyspnea and edema of the ankles. He had dislocated lenses and had worn glasses for fifteen years. He had no history of rheumatic fever.

The family history revealed that his mother was said to have had congenital heart disease; his daughter had dislocation of the eye lens.

Physical examination revealed a well developed, well nourished, white man in moderately acute distress. He had elongation of all extremities and fingers. The blood pressure was 130/40 mm. Hg. The heart rate was 80 per minute. Auscultation of the heart revealed a grade 3 early blowing decrescendo diastolic

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murmur in the aortic area, which was heard best along the left sternal border and was transmitted to the apex. The maximum apical impulse was palpated in the sixth intercostal space at the left anterior axillary line. There were numerous moist rales throughout both lung fields.

The laboratory data were within normal limits. The electrocardiogram showed left bundle branch block and digitalis effect. X-ray of the chest (Fig. 1) showed a grade 3 cardiac enlargement. The left ventricle was the most significantly enlarged portion of the heart. The ascending aorta was markedly and rather evenly dilated. It pulsated tremendously.

The diagnosis of Marfan's syndrome was made. The patient was discharged on July 6, 1955, with no evidence of cardiac failure, but a week later he was readmitted to the hospital with pain in the chest and symptoms of left heart failure. The electrocardiogram revealed a supraventricular tachycardia. The patient failed to respond to efforts to relieve his congestive failure, and he died on the tenth hospital day.

The significant pathologic findings were as follows: The body was that of a thirty-three year old white man, well built and well nourished, weighing approximately 180 pounds. No abnormalities were noted in the head. The chest was symmetrical, well expanded in all directions, and tympanitic. No lymph nodes were palpable in the axilla. The lower border of the liver was palpable three fingerbreadths below the right costal margin. The spleen was enlarged and was palpable one fingerbreadth below the left costal margin. Extremities were equal in length. There was hyperextension of the fingers at the interphalangeal and metacarpophalangeal joints on both sides.

The mediastinum was occupied by a tremendously enlarged heart, roughly globular in shape which weighed 1,000 gm. The epicardium was smooth, glistening and transparent. On opening the cardiac chambers, both the right and left ventricles were dilated and their walls were thickened. The wall of the right ventricle measured 8 mm. in average thickness, and the wall of the left ventricle measured 22 mm. in average thickness. The entire heart was flabby, and multiple sections throughout the myocardium showed it to be a yellowish brown color. On examination of the endocardium of the right ventricle, there were two bar-like, thickened, raised streaks measuring 3 mm. in length. The endocardium of the left auricle was thickened and similarly showed transverse grayish white striations which were most marked above the mitral valve. The aortic ring was dilated. The cusps were soft and elastic, and no fusion at the commissures was noted. The aortic valve allowed four fingers to pass through. The mitral, tricuspid and pulmonary valves were normal. The circumferential measurements were as follows: tricuspid valve, 11 cm.; mitral valve, 9.2 cm.; aortic valve, 10.2 cm.; and the pulmonary valve, 6.8 cm. On taking multiple sections through the coronary arteries they were all found



FIG. 1. Case 1. X-ray of the chest.

to be patent. The root of the ascending aorta revealed an aneurysmal dilatation measuring 7.5 cm. in transverse diameter. On opening the aorta the intima around the coronary orifices showed radiating scars and striations extending for approximately 3 cm. in all directions. The intima about this area also showed several yellow atheromatous plaques. A longitudinal tear measuring 4.2 cm. in length 2 cm. from the right coronary orifice in the intima was found. (Fig. 2.) The margins were sharp and widely separated, exposing the media beneath. Examination of the rest of the aorta showed scattered yellow atheromatous intimal plaques throughout.

On microscopic examination, the epicardium showed accentuation of the mesothelial cells, and there was scattered lymphocytic infiltration, some of which involved the epicardial fat. The muscle fibers appeared hypertrophied, and there was increased space between the fibrils. There were local areas of increased fibrous elements replacing myofibrils. There was thickening of the endocardium, but the area adjacent to the myocardium was loose and almost cystic in appearance. The blood vessels showed only marked congestion. Section of a coronary artery was within normal limits but in the adjacent fat there was a small focal area of hemorrhage. The valves were normal.

There was an aneurysm of the ascending aorta with a 4.2 cm. rent in the endothelium, but microscopically no rupture through the full thickness of the wall was noted. The aortic wall revealed fragmentation of the elastic fibers and cystic medial necrosis



FIG. 2. Case 1. Aorta, showing tear in intima, A, above right coronary ostium, B. The apparent ridge around the left coronary ostium, C, is an artefact due to invagination of the aortic wall.

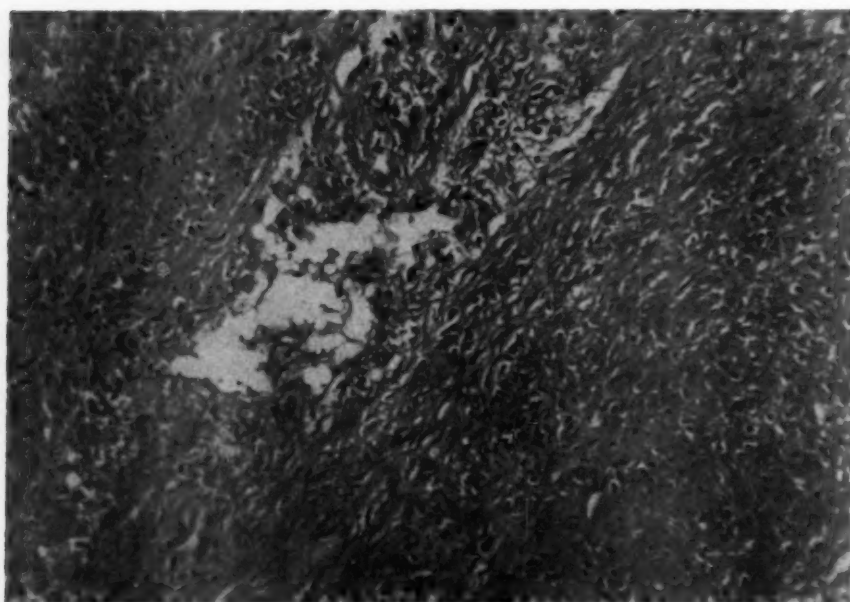


FIG. 3. Case 1. Section of aorta, showing cystic medial necrosis and basophilic fragmentation.

(Fig. 3), which was most marked at the site of the rent. The normal parallel fibers were distorted due to areas of medial necrosis, some of these cystic, others with loose stroma showing basophilic changes. The vasa vasorum were congested and showed no endarteritis obliterans. Congested vessels were also found in the media.

The basic cause of death was the medial necrosis in the aorta, causing aneurysmal dilatation of the aorta and dilatation of the aortic ring with resultant cardiac failure due to aortic insufficiency.

CASE II. This forty-five year old white male pa-

tient (I. K.) was admitted to the hospital on October 4, 1955, with a chief complaint of pain in the left shoulder of six years' duration.

The patient was in good health until 1944 when subacute bacterial endocarditis developed. He was treated in a hospital with penicillin, and was discharged apparently cured. He was told that the infecting organism was a streptococcus. He had never had rheumatic fever. In 1949 the patient noted non-radiating pain in the left deltoid region. He described the pain as "a burning sensation" which lasted for fifteen to thirty minutes at a time, and which came on while he was lying in bed. When the pain appeared he



FIG. 4. Case II. Photograph showing long feet and toes.

would sweat and would notice an increased pulse rate. There was no cough or dyspnea associated with these attacks. Over the next two years the pain increased in intensity, frequency and duration. In 1953 he first noticed that it radiated across the chest to the sternum. He also noticed at this time that exertion and emotional upset would bring on the complaint, although it continued to waken him at night. During the past year (1954) he had been taking nitroglycerin to relieve this pain, and the number of attacks had become less. There were no other cardiac symptoms. In 1929 he had had dislocated lenses, and was operated on for this.

His father died of pneumonia at the age of sixty-nine with a coexistent mitral stenosis. One sister had a pneumonectomy for tuberculosis. His mother, sister and two sons are of the same build and have eye defects of an unknown nature.

Physical examination on admission revealed a tall (78 inches), thin man who was very slender and had long arms and legs, with tapering fingers and toes. (Fig. 4.) Blood pressure was 180/33/0 mm. Hg in both arms. There was normal sinus rhythm, at a rate of 84 per minute. A grade 3 blowing diastolic murmur was audible at the base, maximal in the third intercostal space at the right sternal border. There was also a grade 2 blowing systolic murmur in the same area, and a faint blowing systolic murmur was heard at the apex. The point of maximal impulse was in the seventh interspace at the anterior axillary line. The liver was not enlarged. The lung fields were clear. The peripheral signs of aortic insufficiency were present.

SEPTEMBER, 1957



FIG. 5. Case II. X-ray of the chest. Note enormous ascending aorta (A).



FIG. 6. Case II. X-ray of hands.

The laboratory findings were essentially negative. The electrocardiogram revealed normal sinus rhythm with evidence of left ventricular hypertrophy and strain. X-ray examination of the chest (Fig. 5) showed marked enlargement of the left ventricle. The ascending aorta was enormously dilated and showed a tremendous expansile pulsation. In the lateral view a funnel type deformity of the upper part of the body of the sternum was discernible. X-ray films of both hands demonstrated moderate elongation of the tubular bones, with no other structural abnormality. (Fig. 6.)

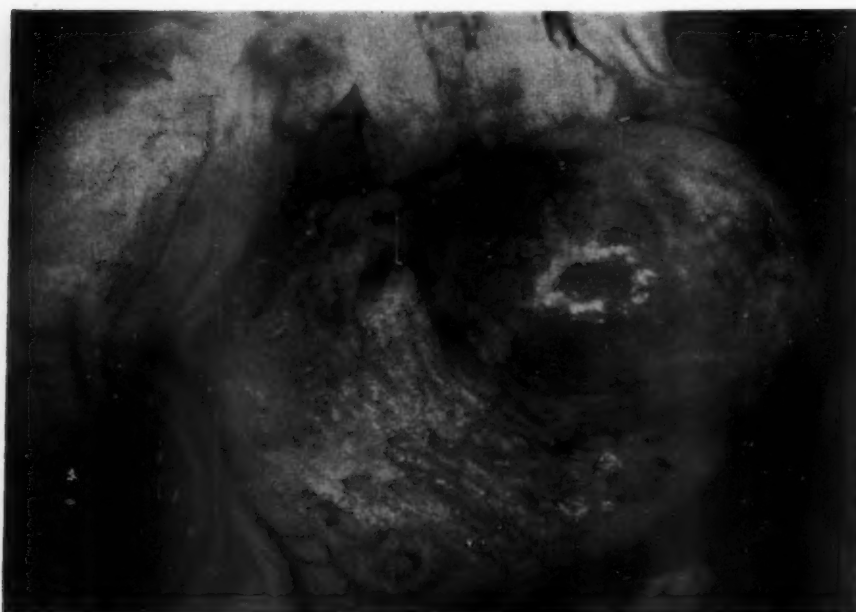


FIG. 7. Case II. Dilated aorta exposed at surgery.

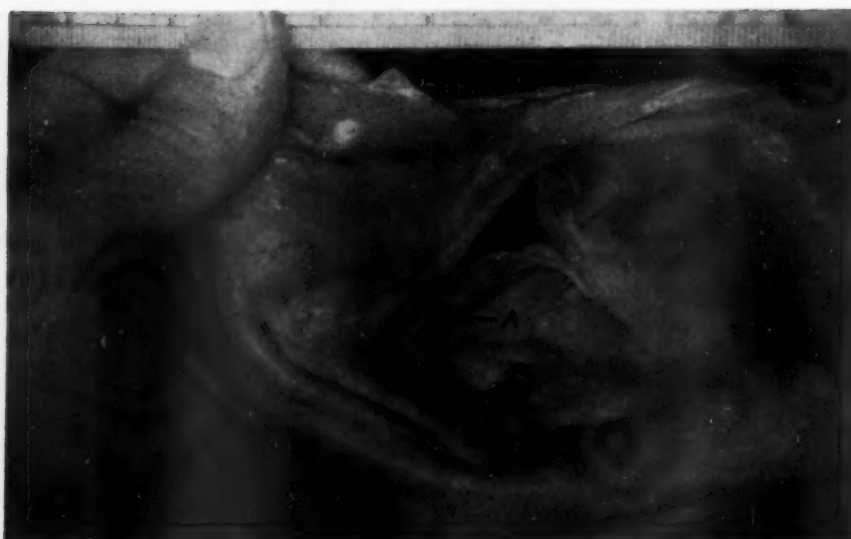


FIG. 8. Case II. Autopsy. Looking at aortic valve from above, showing dilated aortic annulus, and deep-lying sac-like valve cusps, with perforation in left coronary cusp (A).

An attempt was made to treat the aortic insufficiency by placing a nylon ligature around the aortic annulus. Figure 7 shows the enormously dilated ascending aorta at surgery. However, ventricular fibrillation developed during the procedure and the patient died.

The significant pathologic findings were as follows: The body was that of a thin, tall man weighing approximately 160 pounds. There was a transverse thoracotomy incision which was recent. The eyes presented bilateral iridectomy scars. The lens of both eyes could not be seen. Of interest were the extremely long, slender fingers and long toes.

The heart weighed 1,200 gm. The pulmonary

arteries revealed no thrombi or emboli. The epicardium presented some areas of fibrosis, and a few areas of hemorrhage which were probably due to cardiac massage. Examination of the valves of the heart revealed an insufficiency of the aortic valve and a greatly dilated aortic ring. The left coronary artery cusp presented a 3 mm. diameter opening in the edge of the cusp. (Fig. 8.) The aortic valve measured approximately 5.5 cm. in diameter, the insufficient opening measuring 4.5 cm. on each side of the triangular orifice formed by the incompetent aortic leaflet edges. The tricuspid valve measured 4.5 cm., the mitral valve, 5 cm.; and the pulmonary valve, 3.5 cm. in diameter. The myocardium of the right

ventricle measured 0.8 cm. in thickness, and the left ventricle, 2.2 cm. (Fig. 9.) There was gross evidence of hypertrophy and dilatation of both ventricles. The mitral valve was somewhat thickened and fibrotic but there were no nodules or calcification. No bacterial vegetations were noted on any of the valve leaflets, although the perforation in the aortic cusp may have been the residual of his bacterial endocarditis. The coronary vessels showed a moderate degree of atherosclerosis but were patent throughout their entire length. Of note was the fact that the left coronary ostium was 2.5 cm. from the base of the sinus of Valsalva.

The aorta presented a moderate degree of atherosclerosis. At the base of the ascending aorta there was a transverse tear (measuring 1.5 cm.) 1 cm. from the bottom of the sinus of Valsalva, in that portion of the aorta which faced the left coronary aortic cusp. This tear was plugged with some oxycel. There was also a longitudinal tear in the posterior aspect of the pulmonary artery at the base, near the pulmonary valve cusps, which measured 3 cm. in length and was sutured. However, there was a right-angled tear about the midportion of this longitudinally sutured rent, which measured 0.5 cm. and freely communicated with the mediastinum. (These were surgically produced rents). The left and right pulmonary cusps were sutured together at the commissure.

Sections revealed the endocardium to be thickened by fibrous tissue. The myocardium presented patchy areas of fibrosis replacing the muscle fibers which were hypertrophied. The muscle fibers appeared to be separated more than normally from each other by fibrous tissue. The blood vessels were normal. No Aschoff bodies were noted in the sections taken.

The medial portion of the aorta showed disruption of fibers, cystic appearance, hyalinization and hemorrhage. There was a small degree of lymphocytic infiltration in these areas. The vasa vasorum were congested but the vessels showed no pathologic changes. (Fig. 10.)

CASE III. This forty-two year old white woman (D. L.) felt sudden onset of pain in the back of her chest six years ago; this was severe enough to require hospitalization. X-rays and spinal taps were negative. The pain disappeared in a few days and its cause was not determined. On July 1, 1955 the pain recurred in the region of the left scapula. The same night she had an attack of severe precordial pain, dizziness, nausea and shortness of breath. She was taken to a hospital where a diagnosis of pulmonary edema was made. Three weeks later, while recuperating, she had another attack of pulmonary edema. Because of these recurrent attacks and sharp pain in the chest, she was referred to The Mount Sinai Hospital, New York City, in January, 1956. Several tests were made, including cardiac catheterization. Needle pressures at that time were 74/44 in the right brachial artery,



FIG. 9. Case II. Autopsy. Left ventricle cut open to show dilatation and hypertrophy.

and 158/51 in the left brachial artery. A diagnosis of Marfan's syndrome was made, complicated by a dissecting aneurysm of the aorta, and severe aortic insufficiency with cardiac decompensation. The difference between the pressures in the right and left brachial arteries suggested that dissection of the aorta had occurred, partly obstructing the orifice of the innominate artery. In addition, she had congenital dislocation of the lenses, pectus excavatum, arachnodactyly of mild degree and severe anemia.

Physical examination revealed a forty-two year old, pale, white woman. Pectus excavatum of a mild degree was present. There were bilateral basal rales in the lungs. There was some increase in the paraspinal dullness. The heart was enlarged to percussion. Over the aortic area there was a grade 2 to 3 systolic murmur, which was transmitted to the vessels of the neck and heard over the entire precordium. This was followed by a grade 3 to 4 early blowing diastolic murmur which was transmitted along the left border of the sternum to the apex. There was a distinct systolic and diastolic thrill over the left sternal border. The blood pressure was 96/70 mm. Hg in the right arm, and 156/60/0 mm. Hg in the left arm.

Except for a hemoglobin of 10 gm. per cent and hematocrit of 31 per cent, the routine blood and urine

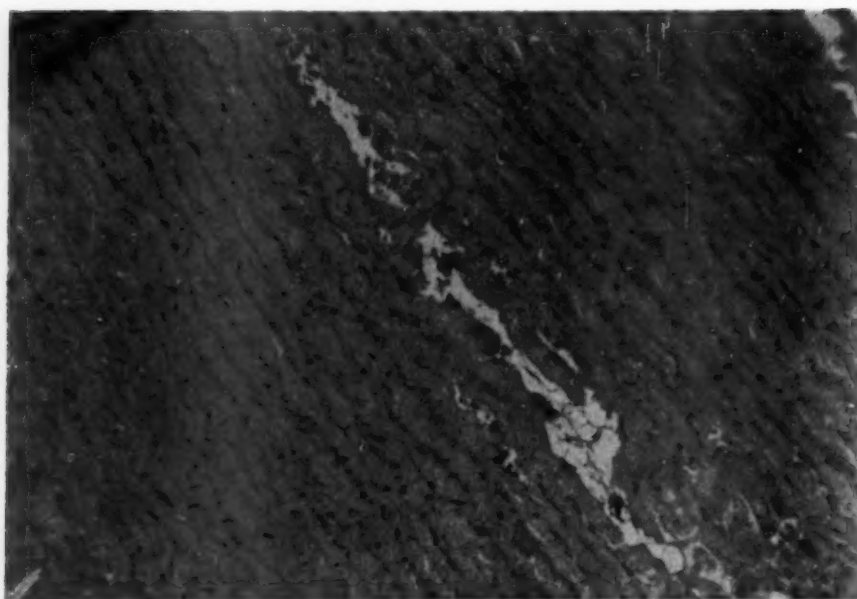


FIG. 10. Case II. Section of aorta showing cystic medial necrosis and basophilic fragmentation.



FIG. 11. Case III. X-ray of the chest.

tests were normal. The electrocardiogram showed left ventricular hypertrophy and strain. Fluoroscopy and x-ray studies (Fig. 11) revealed a grade 3 enlargement of the heart, with a tremendous dilatation of the arch of the aorta which was thought to be due to a dissecting aneurysm. The left ventricle was markedly enlarged. The lung fields were congested, the costophrenic sulci were clear, and both hemidiaphragms were mobile.

The history, physical examination, electrocardiogram, x-ray and fluoroscopy findings pointed to a

diagnosis of Marfan's syndrome, complicated by a dissecting aneurysm of the aorta, and anemia. Aortic insufficiency and congestive heart failure were also present.

Attempts were made to treat the cardiac failure and anemia. Surgery for dissecting aneurysm was considered inadvisable because of the associated problem of severe aortic insufficiency, and recommendations were made to continue on a medical regimen. As far as is known, the patient is still living.

COMMENTS

Although approximately 350 cases of Marfan's syndrome have been reported, comparatively few complete autopsy reports have appeared in the literature. Marvel and Genovese [8], in 1951, collected descriptions of twenty-eight necropsies and added one of their own. Cardiovascular lesions were found in twenty-six of these, including aortic aneurysms in fifteen. Eight of the aneurysms were of the dissecting variety. Left ventricular hypertrophy, which is usually associated with valvular disease, was present in twenty cases. In sixteen patients there were congenital cardiovascular malformations, often multiple. Detailed microscopic studies of the aorta are lacking in fifteen of the twenty-nine necropsy cases.

The present report describes three additional typical cases of Marfan's syndrome, in two of which a complete autopsy was performed.

There is, as yet, no proof of a common pathogenesis of dissecting aneurysm with or without

Marfan's syndrome. As McKusick [9] has suggested, dissecting aneurysm of the aorta may have a varied pathogenesis, some being hereditary, others acquired.

The basic pathologic lesion in the aorta of the patients herein reported was a cystic mucinous degeneration of the media, similar to that described in the literature. It is not difficult to understand how this may lead to massive dilatation of the aorta and the aortic valve annulus, with a resultant insufficiency at the valve orifice even in the presence of normal leaflets. Dissection of the aortic wall may readily occur under these circumstances.

SUMMARY

Three cases of arachnodactyly complicated by aneurysm of the aorta are presented. In two of these cases the autopsy findings are described. Autopsy showed a tear in the wall of the aorta, without dissection in one of our patients. Generalized aneurysmal dilatation of the aorta was present in all three cases, with aortic insufficiency.

Aneurysm of the aorta is a frequent occurrence in patients with arachnodactyly who reach adulthood. Dissection of the aorta may be responsible for early death in these patients. Generalized dilatation of the aorta may lead to aortic insufficiency and death.

Acknowledgment: Autopsy material was made available by the Department of Pathology,

Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa.

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Marfan's Syndrome: Description of a Family*

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McKUSICK [7] has recently comprehensively redefined the Marfan syndrome, which is a genetically determined, dominantly inherited disorder of protean clinical display believed to arise from a connective tissue defect. Salient clinical manifestations include gracile or gangling habitus with long head (dolichocephaly), long, thin extremities (dolichostenomelia), long digits (arachnodactyly), lens dislocation (ectopia lentis), highly arched palate, pectus excavatum ("funnel breast") or pectus carinatum ("pigeon breast"), kyphoscoliosis, dilatation of the ascending aorta with aortic regurgitation, dissecting aneurysm, multiple

hernias and hypermobility of joints. Intelligence is usually normal. The dire cardiovascular defects, in particular, have been emphasized recently [2-4].

The purpose of this report is to record additional experience with the disorder. An instructive kinship recently encountered will be presented. No information illuminating the basic nature of the Marfan syndrome was obtained in this study.

CASE REPORTS

The family tree is shown in the conventional fashion in Figure 1. Defects encountered in each member are listed beneath his position in the pedigree.

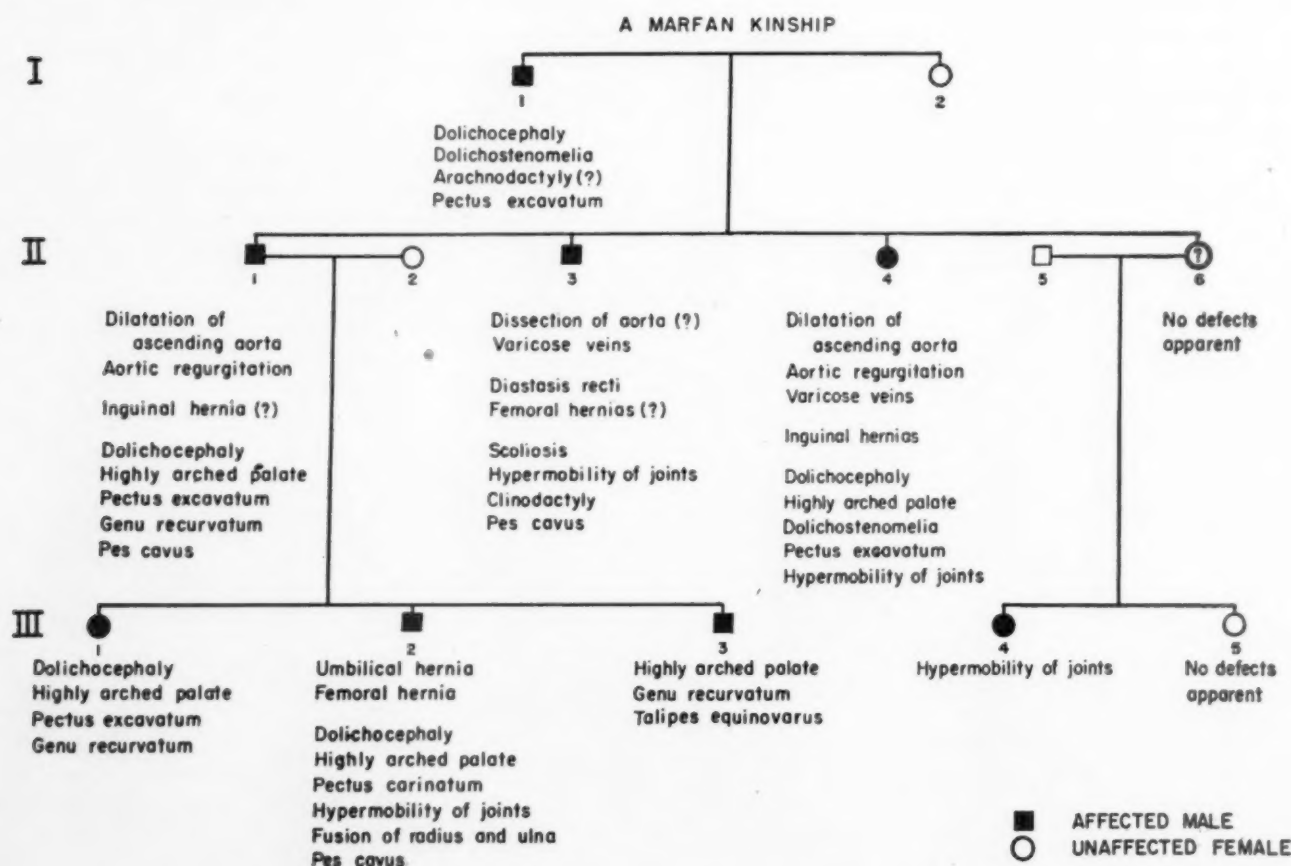


FIG. 1. Family tree. Defects found in each member are listed beneath his position in the tree.

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I 1: G. S. Sr. was probably the progenitor of this Marfan syndrome kinship. He was 6 feet 3 inches in height and weighed only 135 pounds. Family photographs show that he had a narrow face, long arms and legs, and long, tapering fingers. His wife adds that he "had a sunk place in his chest, same as George Jr." (II 1.) He was considered "delicate" by his family throughout life. His vision was normal. The family has no knowledge of hernia, flat foot or any other abnormality. He died suddenly at age twenty-nine following a prolonged illness which was characterized by weakness, ataxia and, toward the end, difficulty in swallowing. He was not short of breath and did not complain of pain in the chest. On the death certificate death was attributed to brain tumor. Autopsy was not performed in the rural Kentucky community where he died.

Both of his parents died late in life, one of infection, the other of heart failure. Three siblings, all heavy, are in robust health in middle-life. One sister, short and heavy, died suddenly at age fifty. Autopsy was not performed. Full investigation of this group and all their progeny has not been carried out and is not planned.

The non-consanguineous widow (I 2) of Individual I 1 is now forty-four years old. She is a healthy round-faced woman of normal body proportions. She has no congenital defects to her knowledge other than myopia, which apparently none of her children have inherited. She has not been examined by the author.

II 1: G. S. Jr. (Cincinnati General Hospital, 134774; The Children's Hospital, 0-14045; Veterans Administration Hospital, 6266) was apparently normal at birth but "outgrew a hernia" as a child by wearing a truss. Funnel breast was found on examination at eight years of age. Examination of the heart showed no abnormality. Chest x-ray and electrocardiogram were likewise normal. The child survived diphtheria at ten, a heart murmur again not being noted; but at age twelve, examination at the time of hospitalization for pharyngitis revealed a "thin," "undernourished," "chronically" ill boy weighing only 62 pounds. The chest was long and narrow, and the sternum "caved in." Vigorous precordial and suprasternal notch pulsations were noted. A soft systolic murmur was heard over the entire precordium, loudest in the second interspace (right or left side not specified) and transmitted to the neck. The "pulmonic closure sound" was described as "booming." An electrocardiogram was again normal, but a "suspicious bulge in the region of the pulmonary conus" was found on roentgenogram of the chest.

The subject enlisted in the Army at age seventeen. (Fig. 2.) At that time he weighed 114 pounds and was 5 feet 8½ inches in height. Vision was found to be normal (as it was throughout life). Moderate pectus excavatum was again noted. A heart murmur was not described. The blood pressure was 118 mm. Hg systolic, 82 mm. Hg diastolic. A chest x-ray upon



FIG. 2. Snapshot of Individual II 1 nine years before death. Note thin face and pectus excavatum. Fingers (poorly shown) were not abnormally long.

induction (Fig. 3) was interpreted as normal but review of this film and one taken four years later showed slight prominence of the pulmonary artery. This may, in part, have been attributable to displacement and rotation of the heart secondary to pectus excavatum.

Six months after enlistment pain and swelling in the right knee occurred following a march. Relaxation of the cruciate ligaments was pointedly noted. A diagnosis of osteochondritis dissecans was made when "joint mice" were seen on x-ray films. Also at this time a systolic murmur was heard in the second left interspace and was ascribed to the deformity of the chest. A diastolic murmur was not heard.

The patient was considered to be unsuitable for military duty because of the knee disorder and was discharged. A subsequent Veterans Administration compensation rating for genu recurvatum and functional cardiac murmur was made. Both defects were adjudged to be developmental or constitutional abnormalities.

At twenty-two years of age the subject was admitted to a hospital for treatment of a severe wrist injury sustained on a punch press. Examination of the heart was not recorded but blood pressure before and during a long operative procedure was essentially normal, 120-156 mm. Hg systolic, 80-100 mm. Hg diastolic. Following this injury the patient worked as a timekeeper.

Four months prior to admission the patient's wife

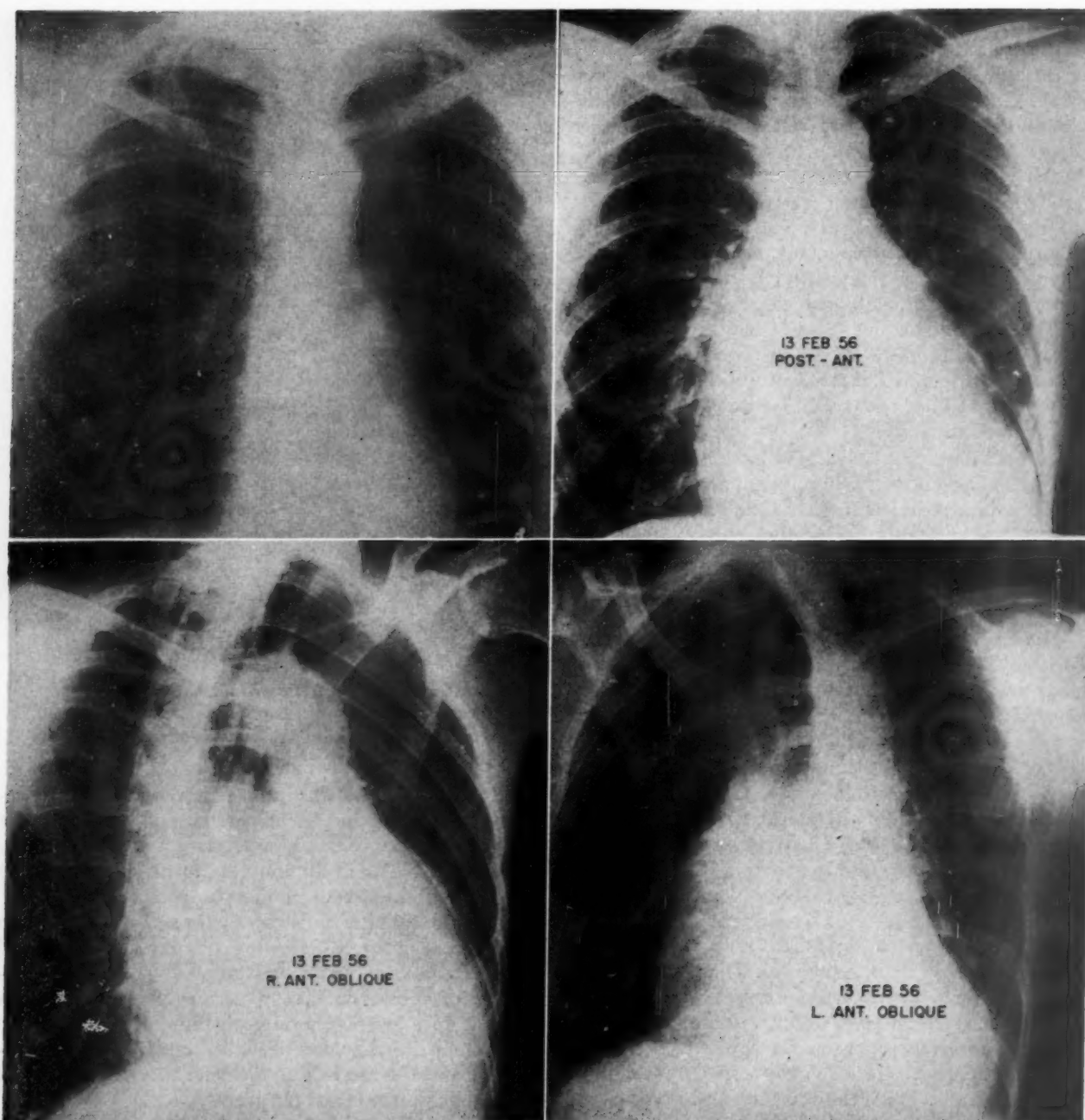


FIG. 3. Individual II 1. The pulmonary artery is somewhat prominent in the early film (upper left, taken in 1946) but this may be due to displacement and rotation secondary to pectus excavatum. A film (not shown) taken four years later was identical in appearance. Films taken shortly before death show generalized cardiac enlargement and prominence of the ascending aorta, which is best seen in the left anterior oblique view.

noted that her husband, now aged twenty-six, was short of breath after sexual intercourse and on subsequent nights soon realized that he could not maintain the torrid three-to-four times a night, three-to-four times a week pace which she insisted they had enjoyed during their seven years of marriage. She initially teased her husband about "getting old" but as post-coital dyspnea and exhaustion increased through subsequent weeks, his wife realized that he was ill. Two months prior to admission the rather discerning

wife refused to have further intercourse because she did not want her husband to die "just like Albert" (II 3). Soon all activity produced shortness of breath. The subject gave up his job four days prior to admission following several bouts of paroxysmal dyspnea and syncope. In the two-week period prior to admission there was progressive swelling of the abdomen and the lower extremities. At no time had the patient experienced pain or a sensation of something "giving away" in his chest.

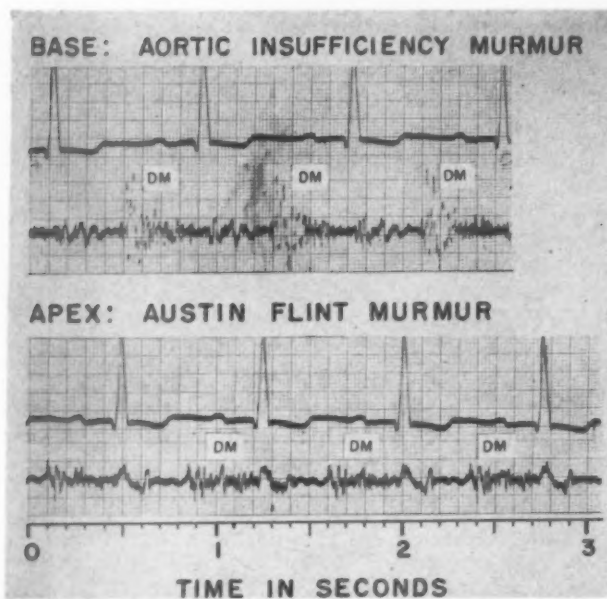


FIG. 4. Individual II 1. Phonocardiogram. Diastolic murmurs (DM) at the base and apex of heart.

Upon examination the patient was found to be in advanced heart failure with dyspnea at rest, orthopnea, heavy sweating, elevated venous pressure (31 cm. of water), prolonged arm-to-tongue circulation time (26 seconds), and soggy lung bases, liver and lower extremities. There was great tumult of the precordium with a diastolic thrill at the base corresponding to a long, loud, blowing diastolic murmur in this area. This murmur was transmitted downward along the sunken sternum. A lower pitched diastolic bruit (Austin Flint murmur) was discovered at the apex. (Fig. 4.) In addition a soft systolic murmur was audible at the apex. Valve closure sounds were loud in all areas. The blood pressure was 132 mm. Hg systolic, 55 mm. Hg diastolic. Durozier's murmur and pistol shot sounds were audible over the femoral arteries and capillary pulsations were increased in amplitude. Electrocardiograms, it is interesting to note, showed clockwise rotation and marked right axis deviation. (Fig. 5.) Pectus excavatum may have contributed to this unusual position of the heart. Roentgenograms of the chest revealed great enlargement of the heart with dilatation of the ascending aorta which, on fluoroscopic examination, showed very forceful, collapsing pulsations. Four curves were present along the left border of the heart, suggestive of rheumatic mitral stenosis. (Fig. 3.)

On further examination the patient was noted to be thin-faced, long-headed and of delicate build. The eyes were normal. The palate was highly arched. The spine was straight and the extremities thin, but the fingers were not abnormally long. The feet, however, were highly arched. Examinations specifically for joint laxity or lens dislocation were not performed as the Marfan syndrome was not given serious consideration during life.

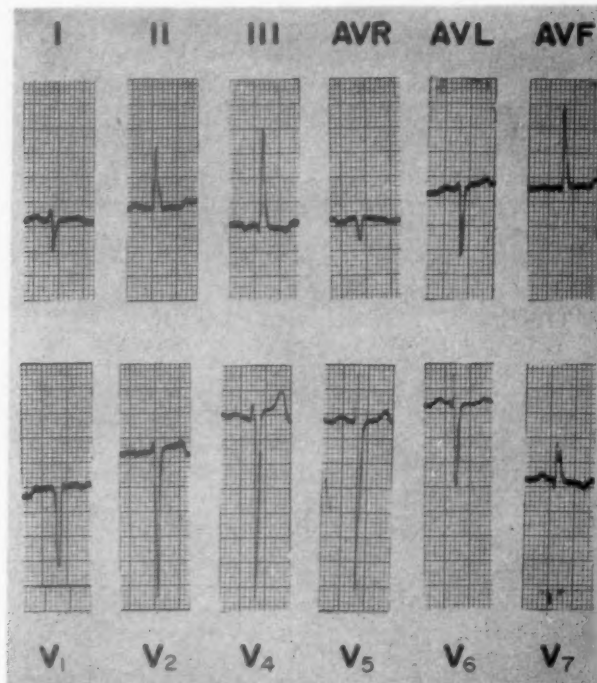


FIG. 5. Individual II 1. Electrocardiogram at the time of final hospital admission, before digitalization. Note the marked degree of right axis deviation and clockwise rotation of the heart.

Heart failure was initially lessened by the use of digitoxin, mercurial diuretic agents, oxygen and thoracentesis, but bouts of apprehension, paroxysmal dyspnea, palpitation and sweating soon returned. The blood pressure varied between 100–160 mm. Hg systolic and 0–50 mm. Hg diastolic. The patient died suddenly as he was being helped onto a bedpan one month after admission.

At necropsy* (limited to an incision of the chest) the ascending aorta (Figs. 6 and 7) was greatly thinned and tremendously dilated, rendering the aortic valve grossly incompetent. The dilatation of the aorta ended abruptly at the origin of the innominate artery, beyond which point the aorta was of normal caliber. The wall of the thoracic aorta was, however, thinner than normal. The dilated ascending aorta, viewed from within, showed irregular loss of intima. This was especially pronounced just above the aortic valve; here the intima was completely absent, leaving ragged scarred media exposed to the bloodstream. The ostia of the coronary arteries were displaced upward, in a fashion typical of the Marfan syndrome, about 1 cm. above the free edges of the baggy valve. Dissection or coarctation was not present. Virtually no atherosclerosis was present in the aorta or in the coronary arteries.

The heart was greatly enlarged, weighing 800 gm. There was extreme left ventricular dilatation, moder-

* Performed by Dr. Boris Gueft.



FIG. 6. Individual II 1. Enlarged heart and dilated ascending aorta. The pulmonary artery is of normal caliber.

ate left ventricular hypertrophy and moderate dilatation of all other chambers. The wall of the left ventricle was 13 mm. in thickness; the wall of the right ventricle was 4 mm. All valves were dilated but were otherwise normal except for moderate rolling of the free borders of the aortic valve. The commissures of the aortic valve were not separated. The valve circumferences were: tricuspid, 14 cm.; pulmonic, 8 cm.; mitral, 11 cm.; aortic, 11 cm. Despite the great weight of the heart and the thickness of the left ventricular wall, both of which were suggestive of long-standing aortic regurgitation, the endocardium of the left ventricle was only slightly thickened. The pulmonary artery was normal.

Microscopically, irregular loss of intima and inner two-thirds of the media of the ascending aorta was found. Fragmentation and cystic degeneration of the elastica was present, with accumulation of considerable toluidine-blue metachromatic mucoid material in the cystic spaces. Few inflammatory changes were seen. The microscopic picture was consistent with the changes seen in Erdheim's cystic medial necrosis of the aorta [5]. No inflammatory changes or fibrosis were seen microscopically in the valves. There was moderate diffuse non-specific scarring in the myo-



FIG. 7. Individual II 1. Diffuse aneurysm of ascending aorta viewed from within. See text for detailed description.

cardium. Other organs showed the expected congestive changes.

In summary, a person with the skeletal and ligamentous defects of the Marfan syndrome died in heart failure secondary to a widening ascending aorta at age twenty-six. There are hints that dilatation may have begun as many as fourteen years earlier, but symptoms of free aortic regurgitation did not evolve until a few months prior to death.

II 3: F. S. (C. G. H. 102272), brother of II 1, first came under medical observation at age nine for treatment of equinovarus and pes cavus defects of the right foot, which had been present since birth. One year later the boy sustained a hyperextension injury of the left knee in a fall and was admitted to the hospital where a blood-filled semitendinosus bursa was excised. An observant intern noted on examination that all ligaments were generally "lax" and the "fingers markedly hyperextensible," with a flexion deformity of the fifth finger of one hand (clinodactyly—a typical Marfan syndrome deformity). General examination showed a "thin, asthenic" lad with poorly developed musculature. Diastasis recti and bilateral femoral bulging on cough were additional findings. The blood pressure was 95 mm. Hg systolic, 65 mm. Hg diastolic. The eyes were described as normal, consistent with later history and examinations disclosing normal vision throughout life.

The subject enlisted in the Army at age seventeen but was soon hospitalized for treatment of the weak foot. On examination at this time the left side of the chest was described as "narrower" than the right, with curvature of the thoracic spine to the left. The heart was thought to be normal. The blood pressure was 104 mm. Hg systolic, 70 mm. Hg diastolic. Varicosities of the superficial veins of the legs were noted. Chest x-rays during service were considered normal but the aortic arch was definitely increased in diameter in the film taken at the separation center, which was the only film available to the author for review.*

* The quality of this photo-fluorogram is too poor for reproduction here.

The subject was discharged as unsuitable for military duty seven months after induction because of enuresis for which organic cause could not be found.

Following discharge he worked steadily as a grinder and, so far as is known, did not consult a physician.

Five days after his marriage at age twenty-two the subject returned home from second-shift work feeling well. He drank coffee with his wife and then retired. It is not known whether coitus ensued, as the subject's wife has not been located. A short time later he arose complaining of precordial chest pain. He soon began to gasp violently and to sweat heavily. He died before a physician could be summoned. Autopsy was not performed.

It is family lore (see Case II 1) that excessive sexual intercourse contributed to the death of this newly-wed young man. The city coroner's unconfirmed death diagnosis was coronary occlusion, but the mode of death equally well suggests dissecting aneurysm of the aorta, which is a common cause of death in subjects with the Marfan syndrome. Defects noted earlier in life clearly mark this person as a victim of the disorder.

II 4: B. S. (C.G.H. 242135; C.H. 27189), sister of II 1 and II 3, was "too small to weigh" at birth and has remained frail and undersized all her life. Bilateral inguinal hernias appeared at age two and a half years. These were subsequently repaired. Upon examination at age six the child weighed only 33 pounds but was 42½ inches in height. The palate was noted to be very highly arched. A systolic murmur was heard over the lower precordium. A few months later a long blowing diastolic murmur was discovered along the sternum. The blood pressure was 118 mm. Hg systolic, 70 mm. Hg diastolic. Because of these findings, together with a history of headache, epistaxis, pharyngitis, failure to gain weight and vague joint pain, it was concluded that the child had rheumatic fever. However, temperature elevation or increase in erythrocyte sedimentation rate was only occasionally recorded on repeated clinic visits. Nonetheless, the girl was confined to a convalescent home for a period of one year. Long head, thin extremities and flabby subcutaneous tissues were findings which were commented upon here. The heart murmurs and blood pressure did not change appreciably. Electrocardiograms, chest x-rays and repeated erythrocyte sedimentation tests were normal throughout this period.

One month after leaving the home, at age eight, swelling of a joint (knee) occurred for the first time but redness or tenderness was not present. Two months later epistaxis returned but laboratory tests again failed to support the diagnosis of rheumatic fever. Prominence of the pulmonary artery and minimal cardiac enlargement were found on x-ray examination of the chest at this time.

The child was not seen again until she was fourteen years old. At that time she was 60 inches in height and weighed 79 pounds. Moderate pectus

excavatum was discovered. The murmurs were unchanged. The blood pressure was 115 mm. Hg systolic, 60 mm. Hg diastolic. Upon cardiac fluoroscopy, the right and left ventricles were thought to be enlarged and the aorta widened and elongated. Left atrial enlargement was not discovered. The physicians at the clinic thought that atrial or ventricular septal defect was the most likely diagnosis.

At the present time, at twenty-two years of age, the subject considers herself to be in good health. She works steadily as an office clerk. She is asymptomatic. On interview and examination she was alert and intelligent, and had a remarkable memory for the details of her own and her relatives' lives. She was frail in appearance. (Fig. 8.) Her height was 60½ inches, span, 60½ inches; weight, 87 pounds. The head was long, face was thin, and the palate was high. She had worn glasses since the age of six because of exophoria, hyperphoria, and hyperopia of 8 diopters in one eye and 4 diopters in the other eye, which were recently reconfirmed by an ophthalmologic consultant who, in addition, found no lens dislocation. Slit lamp examination, however, was not carried out in this subject (nor in subjects II 6, III 2, III 4, and III 5 because the instrument unfortunately was broken on the day when these individuals graciously submitted to interview and examination). The anteroposterior diameter of the chest was remarkably foreshortened with a reverse lordotic curve of the thoracic spine (Fig. 9) and there was slight pectus excavatum. A supernumerary nipple was present. The precordium was moderately active. The heart tones were normal except for an accentuated aortic closure sound. The cardiac rhythm was regular. A short grade 2 systolic murmur was present at the base and a long blowing grade 3 diastolic murmur was present at the base and along the left sternal border. A diastolic murmur was not heard at the apex. The blood pressure was 112 mm. Hg systolic, 60 mm. Hg diastolic. On roentgenographic (Fig. 9) and fluoroscopic examination, the left ventricle, but not the left atrium, was enlarged. Intracardiac calcifications were not noted. The proximal aorta was widened; pulsations were increased in amplitude. Long, attenuated bones (dolichostenomelia) were visible in x-rays but arachnodactyly was not present. Joints were hypermobile. Varicose veins were prominent in the lower extremities.

It cannot be stated with certainty that this person has the cardiovascular defects of the Marfan syndrome, for rheumatic distortion of the aortic valve could account for most of her cardiac findings. It is far from certain, however, that rheumatic fever was present earlier in the life of this closely observed individual. Moreover, the proximal aorta shows a degree of dilatation and expansibility much greater than that which is ordinarily seen in patients with rheumatic aortic regurgitation of moderate degree. The skeletal defects present in the subject mark her un-

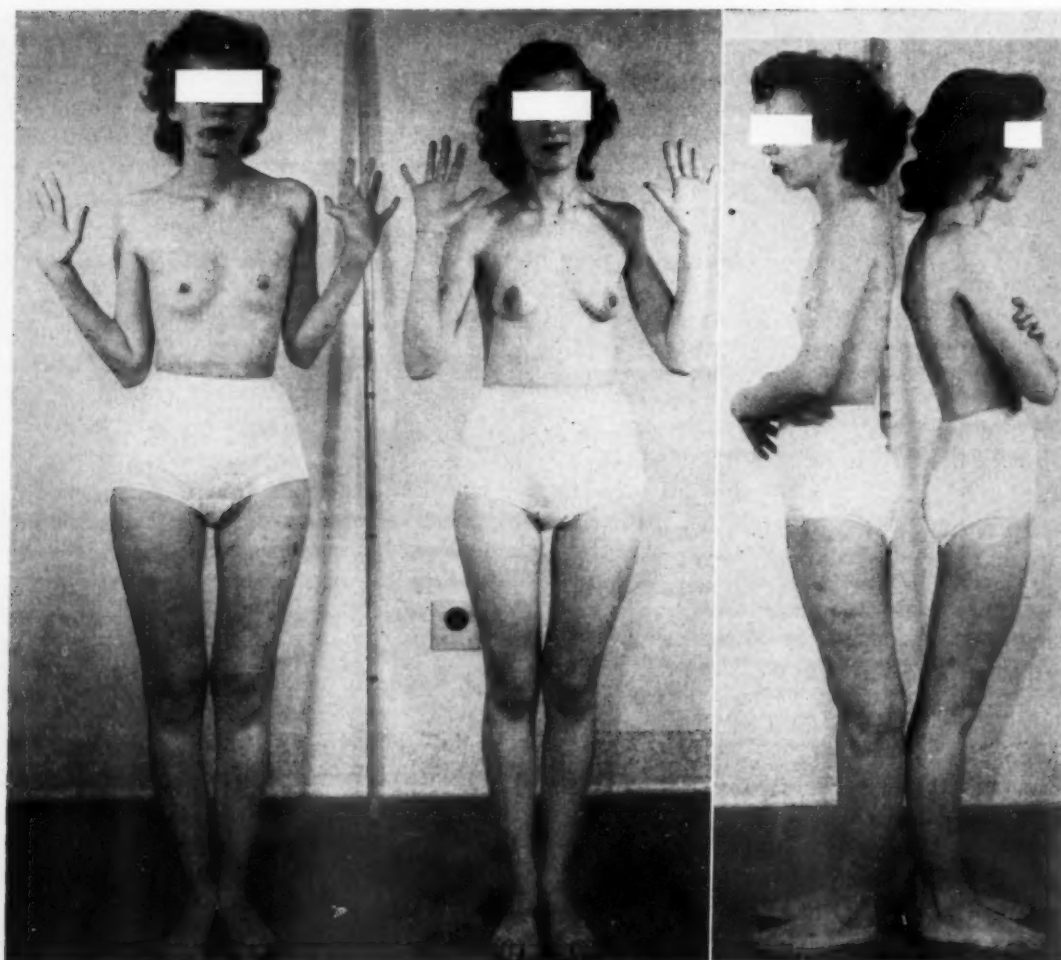


FIG. 8. Individual II 4, left, has mild aortic regurgitation. Marfan defects visible in the illustration include pectus excavatum, thin upper extremities, genu recurvatum and varicose veins. Her sister, Individual II 6, right, is normal on physical examination but may have the disorder in a latent form (see text).

mistakably as an example of the Marfan disorder; it is likely, therefore, that the cardiovascular abnormalities are on the same basis.

II 6: M. C., sister of II 1, II 3 and II 4, has been in good health all her life except for intermittent palpitation and breathlessness at age seventeen. Her doctor discovered a heart murmur (timing uncertain) and interpreted the episode, which spontaneously subsided after approximately one month, as a bout of rheumatic fever. She has never worn glasses.

On examination at age twenty the subject was found to be of symmetric but asthenic build. (Fig. 8.) Her height was 59½ inches, span was 60 inches and weight was 87 pounds. Her eyes were found to be normal by the ophthalmologic consultant. The chest was symmetrical and the spine straight. The palate was normally arched. The heart was not enlarged. The valve closure sounds were of normal intensity. Murmurs were not present. The blood pressure was 108 mm. Hg systolic, 60 mm. Hg diastolic. No hernias were present. The extremities were normal. Joints were not lax. She did not have varicose veins.

It is conceivable that the cardiovascular complaints at age seventeen were the result of sudden minor dilatation or tearing of the ascending aorta and that subsequent repair has abolished the murmur which was present at that time. Against this flight of clinical fancy is the fact that roentgenograms and careful fluoroscopy of the heart at the present time yield no suggestion of widening of the aorta. Nevertheless it is likely that the subject does indeed have the Marfan defect for all her siblings (II 1, II 3, II 4) and one of her daughters (III 4) are affected. Perhaps it will become manifest as she ages.

III 1: T. S. (C. H. 76464), daughter of II 1, weighed less than 3 pounds at premature birth. Retrolental fibroplasia was recognized when she was nine months old. Phthisis bulbi ensued.

Currently, at six years of age, the child is blind but alert and wellspoken. She is of delicate construction. Her height is 43 inches, span is 42½ inches and weight is 34½ pounds. The head is strikingly dolichocephalic. The bridge of the nose is wide and the cheekbones high. The palate is highly arched. There is

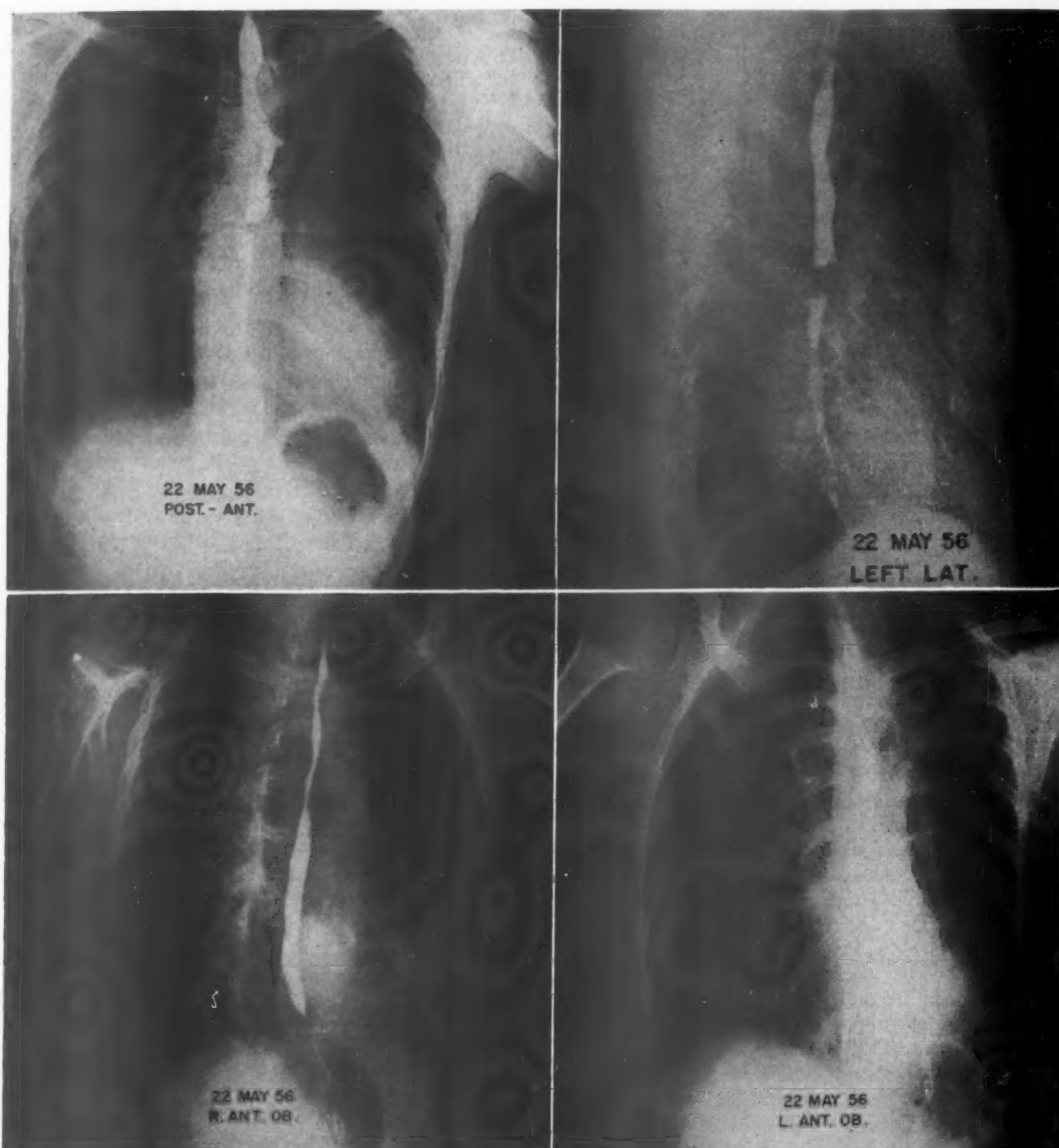


FIG. 9. Individual II 4. Kyphoscoliosis is present, with marked foreshortening of the anteroposterior diameter of the chest. Pectus excavatum is present. The heart is moderately enlarged. Dilatation of the ascending aorta is best seen in the left anterior oblique view.

slight pectus excavatum. The heart is not enlarged or displaced and there are no murmurs. The spine is straight. The arms are long and the hands and feet are big. Arachnodactyly cannot be said to exist, however. Moderate genu recurvatum is present. Hernias are not found.

III 2: G. S. III (C. H. 91297), son of II 1, weighed 5 pounds at birth but the only obvious defect at this

time was cleft palate (also present in the mother, II 2, who was otherwise normal on examination). When the infant was one month old, an incarcerated femoral hernia was repaired surgically. At one year of age the child was readmitted to the hospital for evaluation of retardation in growth. He was 25 inches long and weighed 11 pounds. Micrognathia, pectus carinatum, kyphosis, umbilical hernia, sacrococcygeal dimple,



FIG. 10. Individual III 2. Note the misshapen ears, cross-bite, pectus carinatum, umbilical hernia and hypermobile joints in this underdeveloped three year old child.

bilateral bony fusion of the proximal ends of the radius and ulna, and equinus deformity of the feet with pes cavus of the left foot were further findings. The general conclusion of the hospital staff was that the child had "poor protoplasm." The cleft palate was successfully repaired at age two.

Now three years old, the child (Fig. 10) has a length of 31 inches, a span of $30\frac{1}{2}$ inches, and a weight of 20 pounds—dimensions far below normal for his age—but he is alert and active. Previously noted defects were again found. The face is thin, the head dolichocephalic, the ears misshapen. The upper dental arch is narrow, the lower wide; "cross-bite" malocclusion has resulted. The eyes are normal. Lens dislocation was not discovered by the ophthalmologist. The neck is short. The heart is not displaced or enlarged. Murmurs are not present. The limbs are long and hands and feet big. The mother volunteered that her son was "double-jointed," and, indeed, there is marked hypermobility of the fingers, wrists, knees and ankles.

III 3: D. S., son of II 1, is one year old and is undergoing orthopedic correction of bilateral club foot. Other defects include high palate and marked genu recurvatum. He has no eye disorder, hernia or heart murmur. His general body contours and his state of nutrition are much nearer normal than his scrawny siblings. He weighs only 1 pound less than his three year old brother. Nonetheless, he too clearly has the Marfan disorder.

III 4: J. C., daughter of II 6, age two and a half years, has had normal growth and development since birth. Upon careful examination eye, heart or bone defects were not discovered, but fingers, wrists and knees were found to be strikingly lax. The child is

thus considered to have the Marfan syndrome—a diagnosis one would certainly hesitate to make were it not for the information at hand concerning her forebears.

III 5: B. C., age seven months, daughter of II 6, is normal in every respect. The eyes are without defect. The palate is normally arched. The chest is well-formed. Heart murmurs are not present. Hernias cannot be found. Joint mobility is within normal limits.

COMMENT

This group of subjects exhibits many of the typical skeletal, ligamentous and cardiovascular defects of the Marfan syndrome. Long head, high palate, deformed chest, weak aorta, loose joints and multiple hernias are common features of the disorder.

Eye defects, notably ectopia lentis, were conspicuously absent in this family, but ectopia lentis is not an invariable finding in the disease.

The occurrence of pes cavus in three individuals is unusual. The height of the arch of the foot is principally dependent upon the balance which exists between three structures—the plantar fascia, the gastrocnemius and soleus muscles, and the sling, as it were, about the top of the foot formed by the anterior and posterior tibial muscles. If any of the three structures is weak, the arch will be disturbed. Commonly it is the plantar fascia. This results in flat foot. But muscular underdevelopment and hypotonia are likewise features of the Marfan disorder. Weakness of the calf muscles could well result in pes cavus, as it does in an acquired disease, acute poliomyelitis.

Claw-foot, which resembles pes cavus in appearance, may result from contracture of flexor tendons and plantar fascia following injury in these fragile people. Claw-foot was present in Marfan's original case [6].

It is important to note that individuals afflicted with the Marfan syndrome, although classically tall, thin and "spidery," need not be grotesque or freakish in appearance. The body contours of most of the members of this family are not far from normal. The physician may have to look sharply to discover the skeletal and ligamentous features of the syndrome. The identification of such may dramatically clarify for him a puzzling cardiovascular problem.

Aneurysmal dilatation of the root of the aorta with stretching of the aortic ring and aortic regurgitation, as present in our autopsied case (II 1), has been repeatedly reported in the Mar-

fan syndrome [2-4,7-10]. Dissecting aneurysm is also common in these patients [2-3,11-14]. These two conditions, both of which are basically attributable to the same defect—weakness of the media of the aorta—are the principal lesions found in the cardiovascular system. Defects in the pulmonary artery, in valve structure and in the interatrial septum are less commonly seen. Weakness in the walls of veins which is apparently similar to that found in arteries may result in varicose veins. This was present in two of our subjects. The author knows of no careful histologic study of veins in the Marfan syndrome, however. Indeed, lamentably little is known concerning the basic defect in any tissue. It is thought to be in the elastic fiber but, as many have pointed out, it is hard to reconcile such diverse lesions as ectopia lentis, weakness of blood vessel walls and increase in length of bones on the basis simply of an elastic tissue defect.

In one of our subjects (II 4) a murmur of aortic regurgitation has been present for sixteen years and apparently has not changed much during this time. The aortic regurgitation is believed to be secondary to dilatation of the aortic ring due to the Marfan syndrome. That such a lesion can be tolerated well for a number of years is known. McKusick cites instances of the disorder in which the murmur of aortic insufficiency was present for nine and ten years prior to death in heart failure [3]. The degree of physical activity of the individual probably is important in determining the rate at which dilatation of the aorta occurs. Our patient leads the quiet life of a non-athletic, unmarried office clerk and may continue to do well for some time to come.

On the other hand her two brothers (II 1 and II 3) met early death, one from aortic dilatation, the other possibly from aortic dissection. Both, as men and former soldiers, had undoubtedly led lives physically more strenuous than their sister. This may well have had telling effects on their congenitally weak aortas. Specifically, in each instance vigorous sexual activity may have contributed significantly to progressive stretching or tearing of the aorta. One individual (II 3) died five days after marriage; the other (II 1) first noted dyspnea and fatigue after sexual intercourse. Recent data concerning the astonishing alterations in pulse and respiratory rates which occur during coitus in humans may be pertinent in this connection [15]. Perhaps physical activity such as this should be limited in patients with the Marfan syndrome, especially if evidence that the

aorta is involved is at hand—much as one curtails activity in individuals with saccular or stabilized dissecting aneurysm of the aorta. In the Marfan syndrome a sedentary spinster may outlive an athletic husband.

SUMMARY

A Marfan syndrome kinship involving eight or nine individuals in three generations was found to be notable for defects involving the skeletal and cardiovascular systems but not the eye. Conspicuous abnormalities in the family are dolichocephaly, deformity of the chest, dilatation of the aorta, hypermobility of joints and multiple hernias.

Physical activity, especially sexual intercourse, may have been instrumental in hastening death in two male subjects, while an inactive sister has tolerated mild aortic dilatation well for sixteen years.

Acknowledgment: The author is indebted to Dr. Boris Gueft, pathologist; Dr. Joseph Ginsberg, ophthalmologist; and Dr. Frances Toomey and Dr. Erich Spiro, radiologists, for help in studying this family.

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Review

Renal Involvement in Progressive Systemic Sclerosis (Generalized Scleroderma)*

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PROGRESSIVE systemic sclerosis is now recognized to be a chronic disorder which may affect many organ systems [1-8]. The clinical characteristics of cutaneous, gastrointestinal and cardiopulmonary involvement have been well described [9-12] but the incidence and severity of renal damage in this disease has been appreciated only recently [13-14]. This increasing interest has resulted at least in part from a number of reports of severe renal disease developing in patients with progressive systemic sclerosis who had been receiving either ACTH or cortisone [15-18].

We have had occasion to observe the development of rapidly fatal renal insufficiency and malignant hypertension in seven patients with progressive systemic sclerosis. The clinical and pathologic features of these cases are here recorded, together with the findings in one patient in whom only mild renal dysfunction developed, and one in whom the extensive renal lesions discovered at postmortem examination were not suspected from the clinical course.

CASE REPORTS

CASE 1. C. F., a sixty-six year old white man, a retired contractor, entered Duke Hospital (No. C-74302) on November 4, 1949, with the chief complaint of swollen, painful joints of three months' duration.

The patient reported no serious illness until three and a half months prior to admission when he noted the onset of painless swelling of the lower extremities. At this time too he noted exertional and paroxysmal nocturnal dyspnea. Two weeks later he had pain, redness and increased heat in the joints of the extremities. There was no past history of cardiac or renal disease. The patient had noted increasing pigmentation of his

skin for an unstated period of time and had experienced pain on swallowing, which had been relieved by passage of food into the stomach.

On examination, the patient was poorly nourished and confused. The temperature was normal, the pulse, 80; respiration, 22; and the blood pressure 180/85 mm. Hg. The skin over the extremities and face was tight, dry and edematous, with a diffuse brownish pigmentation. There was generalized muscular atrophy. The eyelids were swollen. A white exudate was seen in the right fundus, with minimal sclerotic changes in the vessels. Moist inspiratory rales were heard bilaterally at the lung bases. The heart was enlarged to the left. The rhythm was regular and the sounds were of good quality. There was a grade 2 apical systolic murmur. The liver edge was felt 7½ cm. below the costal margin. There was 1 plus pitting edema in the lower extremities. The joints of these extremities were swollen, reddened and warm but otherwise were without deformity or limitation in motion.

The specific gravity of the urine was 1.011; the pH, 5; and protein, 2 plus. A rare red cell and white cell were noted in the sediment, and there were many granular casts. The hemoglobin was 12.9 gm. per cent, white blood cell count, 8,800 per cu. mm.; and the platelet and reticulocyte counts were normal. The blood non-protein nitrogen was 69 mg. per cent; serum albumin, 2.6 gm. per cent; serum globulin, 3.6 gm. per cent and phosphorus 4.8 mg. per cent. The electrocardiogram was indicative of an incomplete right bundle branch block. A roentgenogram of the chest disclosed an enlarged heart and infiltrations in both lower lung fields.

The patient was given a low sodium diet. The blood pressure ranged initially around 210/110 mm. Hg. On the fourth hospital day he experienced four generalized convulsions, each beginning with twitching of the musculature of the right face and spreading as a generalized convulsion lasting one to two minutes.

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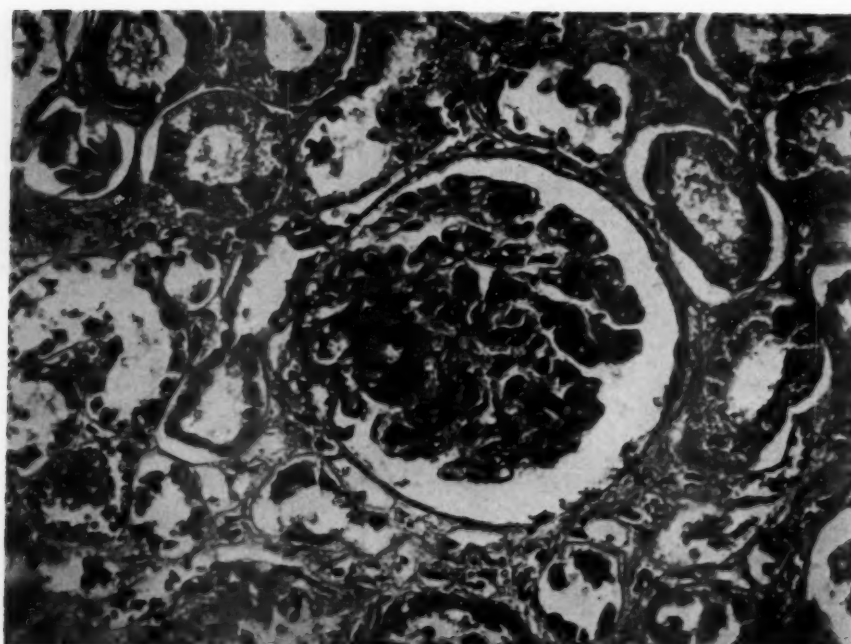


FIG. 1. Case 1. Photomicrograph of glomerulus illustrating focal necrosis of glomerular tuft. Original magnification, $\times 254$.

Intermittent Cheyne-Stokes respiration appeared. Spinal puncture revealed a clear, cell-free fluid, under initial pressure of 175 mm., which contained 76 mg. per cent protein. On the following day pulmonary edema developed, which improved following the use of morphine, digitalis, positive pressure oxygen, and tourniquets to the extremities. His blood pressure at this time was 180/130 mm. Hg and the blood non-protein nitrogen was 101 mg. per cent. The temperature, which had been normal up to this time, now rose to 39°C., and continued thereafter at levels of 39 to 40°C. The patient became incontinent of urine and on the sixth day he lapsed into shock. Blood pressure readings were as low as 60/40 mm. Hg. The pulmonary edema continued and the patient was given hypertonic glucose solution, salt-poor human serum albumin and adrenal cortical extract. While the blood pressure returned to levels of 152/96 mm. Hg, the urinary output on this day, obtained by catheter, was but 115 ml. On the seventh day the patient had another convulsive seizure and died shortly thereafter. On this final day no urine had been obtained from the catheter and the level of blood non-protein nitrogen was 180 mg. per cent. Blood pressures were recorded as low as 90/60 mm. Hg.

On pathologic examination (Autopsy No. 5925) each kidney weighed 170 gm. There was some diminution in the thickness of the cortex. There were a few hemorrhagic areas, measuring up to 8 mm. in greatest dimension, located in the cortex and beneath the mucosa of the renal pelvis. Microscopically, the most conspicuous changes were related to the blood vessels. The interlobular arteries were markedly sclerotic. The lumens were greatly narrowed and obliterated at

times by fibrous thickening of the intima. The fibrous tissue was fairly cellular and compact. The internal elastic membrane was variously frayed, reduplicated and occasionally disrupted. The media, in some areas, had become atrophic. Many afferent arterioles were necrotic. The landmarks of the walls were obscured by eosinophilic fibrillar material which enmeshed numbers of erythrocytes, nuclear detritus, platelets and unidentified hyaline substance. With phosphotungstic acid-hematoxylin stain, both the homogeneous and fibrillar material were found to resemble fibrin. The process of necrosis extended into segments of affected glomeruli. (Fig. 1.) Some of these glomeruli were greatly engorged with blood. In a few instances necrosis was taking place in the internal portions of the sclerotic arteries as well. In one hilar branch of the renal artery a dissecting aneurysm was present. The other branches were not involved and revealed only reduplication of the internal elastic lamella. Small areas of recent cortical infarction were present. A similar pattern of arteriolar and parenchymal necrosis was found in the pancreas.

Summary: A sixty-six year old man with progressive systemic sclerosis of at least three months' duration was found to have scleroderma, hypertension, retinopathy and congestive heart failure, together with proteinuria and increased blood non-protein nitrogen. While hospitalized he had several convulsive seizures, pulmonary edema developed and, coincident with a period of shock, he lapsed into acute renal insufficiency, dying on the seventh hospital day.

The kidneys presented extensive vascular damage with internal thickening of interlobular arteries and necrosis of afferent arterioles extending into segments of glomeruli. Material resembling fibrin was found deposited in the vessel walls. A dissecting aneurysm was noted in a hilar branch of the renal artery.

CASE II. V. M., a forty-four year old white housewife, was admitted to the Clinical Center of the National Institutes of Health (No. 00-08-23) on November 30, 1953, with the chief complaint of painful stiffness of the fingers, shoulders, knees and ankles since June, 1953.

Soon after the appearance of these symptoms the patient noted progressive tightening of the skin over the extremities, face and trunk, and the development of Raynaud's phenomenon. She received a variety of medications for "arthritis" without significant improvement. In October, 1953, she received ACTH for several weeks and there was considerable relief of pain and stiffness. On corticotropin, however, a violent pustular acne developed; the hormone was discontinued and the patient given hydrocortisone, which she received during the month of November, 1953, but there was little symptomatic relief. There had been a weight loss of approximately 18 pounds during the past one and a half years.

On examination the patient was well developed and alert. The temperature was normal, the pulse, 96; and the blood pressure, 114/66 mm. Hg. Marked pustular acne was noted on the arms, chest, face, chin and neck, with venous telangiectasia of the face and chest. There was considerable hardening and thickening of the skin of the fingers, forearms, face, chin and neck; the skin of the chest, back and abdomen was of fairly normal consistency. There was a diffuse increase in pigmentation and spotty vitiligo with non-pitting edema of the hands. The lungs were clear and the heart of normal size with regular action. There was considerable stiffness of the fingers with limitation in the closure of the hands, together with stiffness and limitation of shoulder motion in all directions. The knees were slightly swollen and there was a patellar click on the right knee but no unusual joint redness or warmth.

The urine analysis was normal. The hemoglobin was 12.5 gm. per cent and the hematocrit, 41 per cent. The white blood cell count was 14,400 per cu. mm. and the differential count was normal. Blood chemical determinations included normal values for urea nitrogen and sugar. The total protein was 6.6 gm. per cent (2.4 gm. per cent albumin, 4.2 gm. per cent globulin). The initial electrocardiogram disclosed abnormal T wave changes which were characterized by inversion of the T wave in leads III and V 1-3. X-ray films of the chest and the bony structures of the extremities were considered within the range of nor-

mal. The esophagus was found to be dilated and there was absence of normal peristaltic activity.

The patient was provided with a regular diet. The temperature, which had been normal on the first hospital day, soon began to rise regularly to levels of 38°C. Blood and urine proved sterile on numerous cultures. A cough developed which was productive of mucopurulent sputum, culture of which revealed *S. albus* and *H. influenzae*. The fever persisted during the course of and following the discontinuation of penicillin and streptomycin. The patient noted considerable increase in the stiffness of her joints and development of intermittent edema of the ankles. This was associated with increased stiffness and tightening involving the face, neck and extremities. There was a fall in serum albumin level to 1.8 gm. per cent. The globulin was 4.5 gm. per cent. The urine remained free of protein, and the specific gravity ranged as high as 1.024. Four days prior to death the patient had a sensation of gagging in the area of the oropharynx, which resulted in considerable difficulty in swallowing solids or fluids. Cortisone was given for three days at the beginning of the twelfth hospital week, in a daily dose of 100 mg. The marked weakness and gagging persisted, however, and the patient died suddenly. The blood pressure had ranged from 110-132/50-74 mm. Hg. Urine output on day prior to death was 472 ml. The concentration of blood urea nitrogen was 41 mg. per cent.

On pathologic examination (Autopsy No. A54-7) the kidneys were of normal size. The surfaces were pale and were devoid of hemorrhages. The cortex was of normal width and the corticomedullary demarcation was distinct. Microscopic examination disclosed widespread and severe, although focal, lesions of vessels and parenchyma. The vessels involved were primarily afferent arterioles and glomerular capillaries, although some arcuate and interlobular arteries and interstitial arterioles were also affected. Vessel walls were necrotic and impregnated with fibrin, their lumens occluded by fibrin clot. Focal infarction of the glomeruli was a characteristic feature. Some of the arteries presented focal areas of fibrosis; these were principally intimal, their appearance suggesting healing of preceding lesions. There was severe hyaline droplet degeneration of the collecting tubules. (Fig. 2.) Inflammatory reaction was conspicuously lacking. In addition to this involvement of renal vessels, necrotic and thrombotic changes were present in the arteries, arterioles and capillaries of the myocardium, pancreas, adrenal and sympathetic ganglia.

Summary: A forty-four year old woman with scleroderma of nine months' duration died within three months after manifestations of a progressive systemic illness with fever, dysphagia and arthritis developed. Pathologic examination disclosed extensive renal lesions which were characterized by acute necrosis and thrombosis

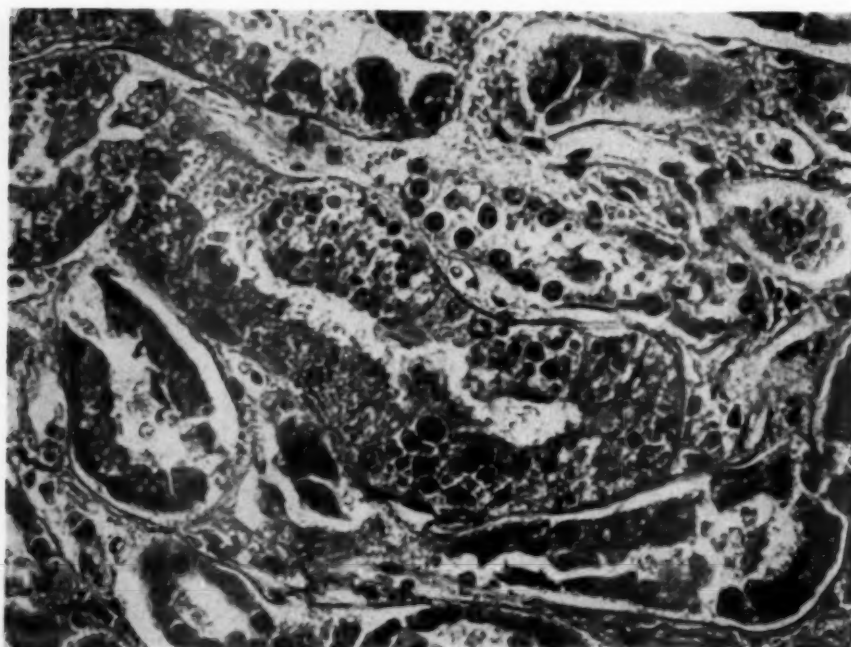


FIG. 2. Case II. Photomicrograph illustrating hyaline droplet degeneration in collecting tubules. Original magnification, $\times 385$.

of the intrinsic arteries and afferent arterioles, with focal necrosis of glomeruli and severe degenerative changes in the tubules. Neither hypertension nor renal insufficiency had developed during the clinical course.

CASE III. M. B., a twenty-six year old white housewife, was admitted to the Maxwell Air Force Base Hospital (Register No. 102-183) on July 6, 1954 following a convulsive seizure.*

The patient had been well until 1951, when there was marked color changes in her legs on exposure to cold. In June, 1952, she noted swelling and stiffness of her hands and feet, and general malaise. In a matter of months the skin of her hands and feet became red and shiny. She received lipoadrenal extract and there was some improvement in her condition. By October, 1952, the patient had marked stiffness in her hands and at that time she was treated with thyroid extract but there was no relief. Beginning December, 1952, she received cortisone for two months, at the end of which time orthopnea developed. The drug was discontinued and the orthopnea cleared. She was admitted to the Clinical Center of the National Institutes of Health (No. 00-02-41) in August, 1953, where she remained for a period of four months. She was noted to have generalized thickening of the skin. The blood pressure was 100/60 mm. Hg. Sibilant rales were heard at both lung bases. The heart was normal except for an apical systolic murmur. There were contracture deformities of the proximal interphalangeal joints in both hands, with limitation of motion of the fingers. Marked limitation of motion was

* This case has been reported independently [19].

observed in both elbows as well as in the shoulders, hips, knees and ankles. Several urine examinations were normal, as were the blood count and blood urea nitrogen concentration. Attempts were made to alter the course of her disease with thyroid and antithyroid substances without notable effect. Following her discharge there was little change in her condition until July, 1954. Early in the month the patient experienced some blurring of the vision and on July 6, 1954, puffiness of her eyelids developed. On that day she suddenly lost consciousness and was brought to the Maxwell Air Force Base Hospital, where she was observed to have a grand mal seizure.

At the time of admission the patient was semicomatose. The blood pressure was 170/130 mm. Hg. The skin was smooth and shiny over the fingers, and dark and thickened over the hands, arms, face, chest and legs. There were whitish exudates in both fundi, and narrowing and tortuosity of the arterioles was noted. The heart was of normal size and there was an apical systolic murmur. The previously mentioned joint changes were again noted.

The urine contained 4 plus protein and there were 3 to 5 white blood cells, 7 to 9 red blood cells and 1 to 2 granular casts per highpower field. The hematocrit was 43 per cent, the white cell count was 24,500 per cu. mm. with 90 per cent neutrophils. Lupus cell preparations were negative. The blood urea nitrogen concentration was 33 mg. per cent; the serum albumin, 3.2 gm. per cent and the globulin, 3.4 gm. per cent. Roentgenogram of the chest appeared normal. An electrocardiogram revealed sinus tachycardia with depressed S-T segments. Lumbar puncture disclosed clear cerebrospinal fluid under normal pressure.

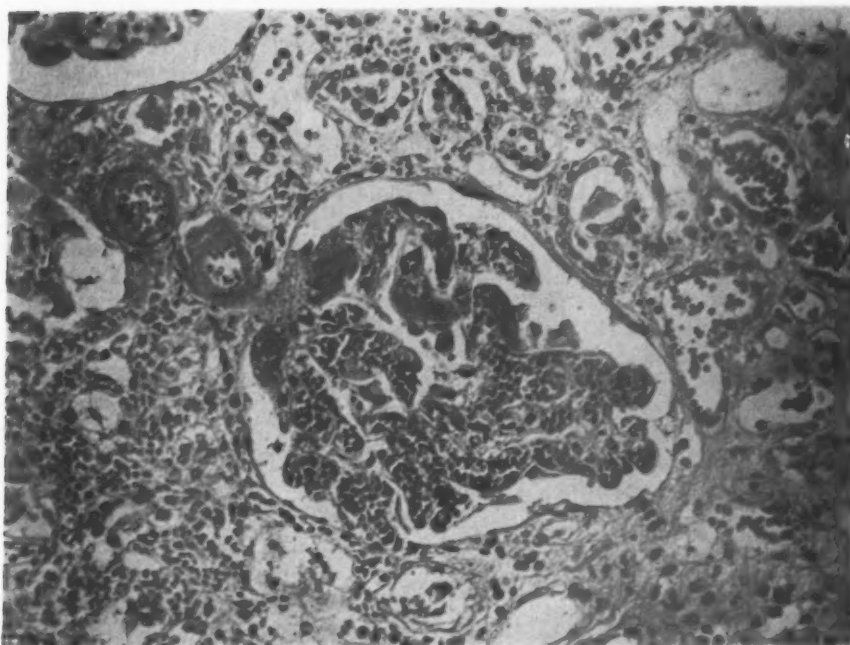


FIG. 3. Case III. Photomicrograph illustrating focal fibrinoid necrosis of afferent arterioles and glomerular capillaries. Original magnification, $\times 205$.

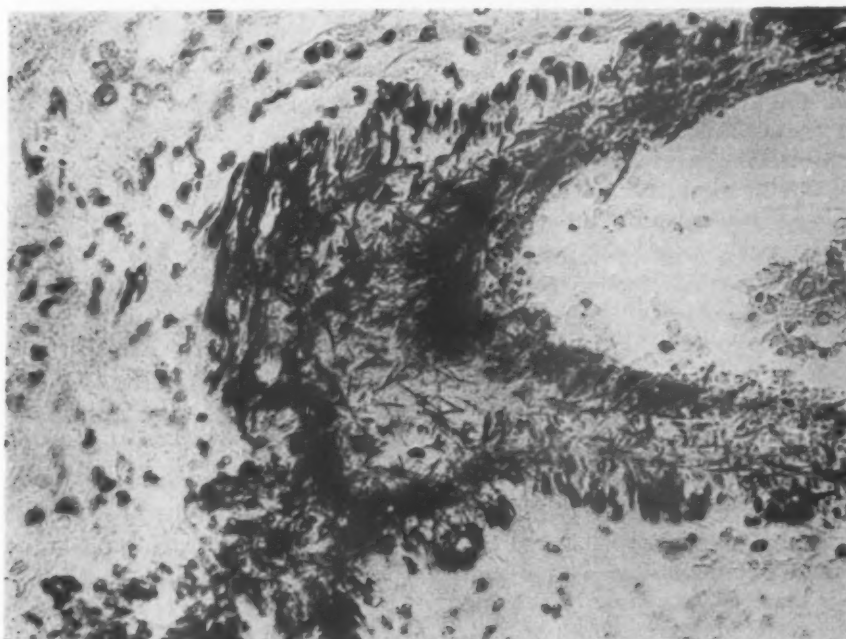


FIG. 4. Case III. Photomicrograph of portion of interlobular artery, stained with phosphotungstic acid-hematoxylin, illustrating fibrinous character of the intramural fibrinoid material. Original magnification, $\times 385$.

The patient remained comatose during the first day in the hospital and, despite administration of paraldehyde and 50 per cent magnesium sulfate, she had additional convulsions. The blood pressure continued to rise to levels of 250/150 mm. Hg. Cheyne-Stokes respiration developed. Following intravenous administration of hydralazine hydrochloride (apresoline®), the blood pressure fell slightly. She received apresoline for the next five days with blood pressure maintained

around 170 systolic mm. Hg. The patient regained consciousness and was able to take food by mouth. After six days, however, she had another convulsion and the blood pressure rose to 240/150 mm. Hg in spite of continued administration of apresoline. At this point melena developed, and the hematocrit was found to be 29 per cent. The apresoline was discontinued and in its place treatment with alkavervir (veriloid®) begun. The systolic blood pressure was

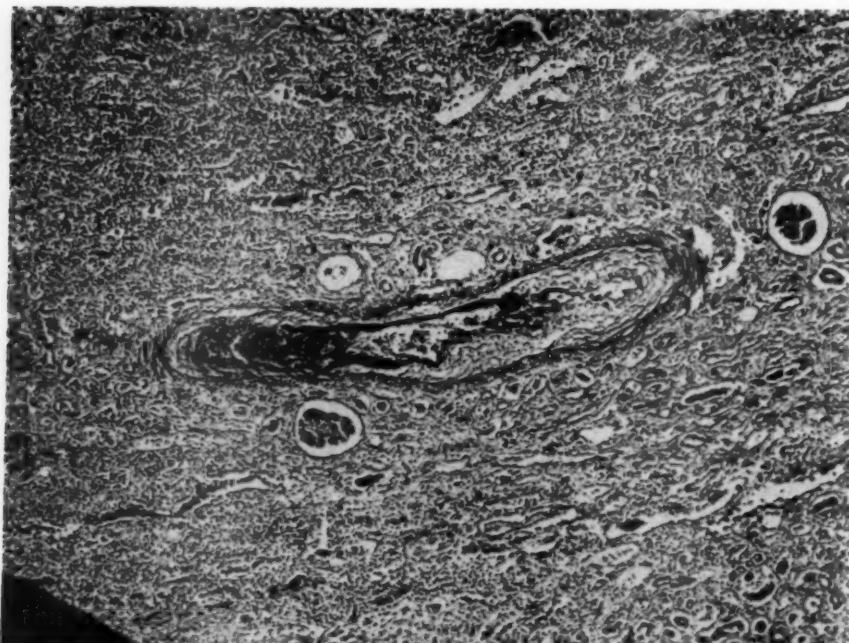


FIG. 5. Case III. Photomicrograph of interlobular artery stained with orcein and hematoxylin-eosin, illustrating fibrous intimal thickening and fibrinoid necrosis. Original magnification, $\times 55$.

now maintained below 200 mm. Hg but the course was steadily downhill. On the seventh hospital day the blood urea nitrogen measured 69 mg. per cent and the hematocrit, 16 per cent. She received 1,300 ml. of whole blood. Urine output diminished steadily. On the ninth hospital day the blood urea nitrogen was 102 mg. per cent (later rising to 141 mg. per cent), and the measured urine output was 16 ml. The patient died on the seventeenth hospital day, having excreted only 375 ml. of urine in the eight days prior to death.

On pathologic examination (Autopsy No. A55-47) the right kidney weighed 175 gm. and the left 170 gm. The surfaces were smooth and the section a mottled reddish-white. On microscopic examination widespread vascular lesions were found, involving interlobular arteries, afferent arterioles and glomerular capillaries. There was focal necrosis of the glomerular capillaries and afferent arterioles. The lumina were filled with thrombus material composed of compact hyaline eosinophilic material and a few red cells. (Fig. 3.) On phosphotungstic acid-hematoxylin staining, this material, which was present in the wall of other vessels as well as in the glomeruli, appeared blue and had the retiform fibrillar character of fibrin. (Fig. 4.) Portions of the vessel wall so affected were necrotic. There was thickening of the intima by cellular fibrous tissue and mononuclear (endothelial) cells, and disruption, reduplication and fraying of the elastica. (Fig. 5.) There were widespread although focal infarctions of the cortex. In some of these areas there was early softening with infiltration of polymorphonuclear leukocytes, in others there was considerable hemorrhagic extravasation as well. Similar

arteriolar lesions were present in the pancreas. A hemorrhagic ileitis was the apparent basis for the gastrointestinal bleeding.

Summary: A twenty-six year old woman with diffuse scleroderma of three years' duration had convulsive seizures and was found to have severe hypertension, retinopathy and proteinuria, with slightly elevated blood urea nitrogen for the first time seventeen days before death. Coincident with the administration of hydralazine and later of alkavervir there developed massive gastrointestinal tract hemorrhage, followed by renal shutdown and death. Pathologic examination revealed extensive necrosis and thrombosis of the smaller renal arteries and arterioles, with widespread focal necrosis of the cortex.

CASE IV. G. D., a fifty year old white insurance man, was admitted to the Georgetown University Hospital (No. 61457) on December 21, 1954 two days following the onset of convulsions.

The patient had been in good health until two years before admission when arthritis of the hands developed. A year later he noted thickening and coldness of the skin of the hands and forearms. When examined two months prior to admission he was found to be normotensive (120/70 mm. Hg). The patient was given phenylbutazone (butazolidin®) at that time, receiving a daily dose of 0.2 gm. and there was some improvement in the "arthritis." A month thereafter he underwent bilateral cervical sympathectomy.

Two days before admission headaches developed, he had several convulsive seizures and lost consciousness. There was no past history of hypertension or renal disease.

On examination, the patient was stuporous. The blood pressure was 220/120 mm. Hg. The skin over the hands, forearms, face and lower legs was thick and tight. The pupils were unequal and reacted sluggishly to light. The fundi displayed narrowing of the arterioles with nicking, and there were hemorrhages and exudates. There was cardiomegaly and a gallop rhythm. Moist rales were present at the lung bases.

The urine specific gravity ranged from 1.005 to 1.015. Qualitative protein reactions were 1 to 2 plus, total excretion was 0.7 gm. protein per twenty-four hours. The sediment contained occasional red blood cells, white cells in clumps, and granular, hyaline, and red cell casts. No "glittering leucocytes" [20] or doubly refractile bodies were demonstrable. The urine proved sterile. The hematocrit was 32 per cent, the reticulocyte count was 2.8 per cent and the white blood cell count was 5,900 per cu. mm. with 68 per cent neutrophils, 15 per cent lymphocytes, 9 per cent band forms, 6 per cent monocytes and 2 per cent eosinophils. The blood urea nitrogen concentration was 44 mg. per cent; serum albumin, 3.3 gm. per cent and serum globulin, 3.3 gm. per cent. The electrocardiogram was normal. Chest x-ray revealed perihilar fibrotic changes bilaterally; the heart appeared of normal size. Esophagram was normal. An electroencephalogram disclosed low voltage fast activity with a bitemporal focus. Needle biopsy of the kidney was performed. The vascular lesions which were found are noted in the summary.

The patient was given cryptenamine (unitensin®) intravenously at the time of admission, the blood pressure falling to 150/80 mm. Hg. Later in the day he experienced a generalized convulsion. The spinal fluid was found to be clear and cell-free; the initial pressure was 180 mm. water and the protein concentration was 150 mg. per cent. On the following day he was given pentolinium tartrate (ansolysen®) 120 mg. per day and reserpine (serpasil®) 0.75 mg. per day, these drugs being continued until the nineteenth hospital day, when he was given alkavervir (veriloid), 9 mg. per day. While there was some diminution in the arterial pressure, the patient continued semicomatose, becoming increasingly oliguric. Daily urine outputs were less than 400 ml. The level of blood urea nitrogen rose to 105 mg. per cent. The patient's blood pressure was 200/100 mm. Hg on the twenty-third day, when he again had generalized convulsions. He died three days later.

On pathologic examination (Autopsy No. 55A21) the kidneys weighed 165 and 170 gm. The cortical boundaries were poorly demarcated. There were three areas of hemorrhagic infarction, averaging 10 mm. in diameter. Vascular lesions of several sorts

were found in the kidney. All the interlobular arteries had a marked degree of sclerosis. Their intima was greatly thickened, at the expense of the lumen, by laminated fibroelastic tissue. In some of these arteries, basophilic interstitial mucoid material was present. The internal elastic lamella was reduplicated and frayed. In places, the media had become atrophic. In some of the arteries a coagulum of hematic elements—fibrin, red cells and amorphous material (platelets)—occupied the lumen. In one or two places the wall of the vessel was necrotic too, and fragmented nuclear material was present within it. The walls of several juxtamedullary arterioles were necrotic and infiltrated with fibrillar eosinophilic material resembling fibrin. There were small areas of cortical infarction, and in one of these, calcification of the necrotic tissue was noted. This calcification involved the infarcted glomerulus as well as the tubules. There was little glomerular alteration in the viable portions of the cortex. Proliferative lamination of the intima and areas of arteriolonecrosis and thrombosis were also noted in the vessels of the spleen, pancreas and adrenals.

Summary: A fifty year old white man presenting a two-year history of scleroderma with joint complaints had convulsions two months following institution of phenylbutazone and one month following bilateral cervical sympathectomy. He was found to have marked hypertension, diffuse scleroderma, retinopathy, cardiomegaly with gallop rhythm, and bilateral rales. There was an anemia of moderate degree, proteinuria, abnormal urinary sediment, elevated blood urea nitrogen and perihilar pulmonary fibrosis. Treatment with a variety of antihypertensive agents failed to avert progressive renal failure, additional convulsions, and death in twenty-three days. Examination of the kidneys disclosed extensive vascular lesions, consisting of sclerosis of interlobular arteries, necrosis of the arteriolar walls, and areas of cortical infarction.

CASE V. J. H., a forty-five year old white housewife, was admitted to the Georgetown University Hospital (No. 62513) on February 6, 1955 with a history of high blood pressure, arthritis and tightening of the skin.

The patient had been well until two years previously, when puffiness of the eyes developed and she was found to be hypertensive. She was given a diet with low salt content. A year later she noted increasing stiffness of the fingers and swelling of the hands, later replaced by a gradual thickening of the skin over the hands and forearms. Her hands turned a mottled blue on exposure to cold. Beginning five weeks before admission she was given cortisone and pentolinium tartrate (ansolysen). Three weeks later persistent occipital

headaches with blurring of vision developed. The patient had had hypertension in the last trimester of her only pregnancy, eleven years before. There were no other findings of toxemia and the blood pressure returned to normal levels postpartum. There was no history of renal disease or of cardiac insufficiency.

The patient appeared chronically ill and pallid. The temperature was normal, the pulse 110, blood pressure 180/110 mm. Hg. The skin was tight, thick and shiny over the hands and forearms, about the eyes and mouth, and over the nose. Examination of the fundi disclosed blurring of the discs, with arteriolar narrowing, hemorrhages and exudates. There were a few scattered rales at both lung bases. The heart was enlarged and there were no murmurs. There was limitation in flexion and extension of the fingers and elbows.

The urine specific gravity ranged from 1.005 to 1.013. There was a qualitative proteinuria of 1 to 3 plus. The protein excretion totalled 1.2 gm. per twenty-four hours. There were many granular and hyaline casts as well as broad renal failure casts. There were 6 to 20 white blood cells per high power field in occasional clumps. Sternheimer-Malbin stain revealed the presence of "glittering leucocytes" [20]. The hematocrit was 27 per cent, red cell count, 2,900,000 per cu. mm., and white cell count, 12,000 (77 per cent neutrophils, 13 per cent lymphocytes, 6 per cent monocytes, 4 per cent eosinophils). At the time of admission the blood urea nitrogen concentration was 74 mg. per cent. The electrocardiogram revealed inverted T waves in the precordial leads, with S-T segment depression. X-ray examination of the chest disclosed bilateral pulmonary fibrosis with cardiac enlargement and tortuosity of the aorta. The esophagus and upper gastrointestinal tract appeared normal.

The patient was given a diet with daily sodium content of 200 mg. and liberal quantities of fluids, without increase in the urinary output. In a period of two days she received 320 mg. of hydrocortisone and 120 mg. of hydralazine (apresoline). Six days following discontinuation of these medications a diastolic gallop and pulmonary rales developed. The daily urinary output decreased steadily from a high of 875 ml. and on the ninth hospital day was but 145 ml., at which time the blood urea nitrogen was 167 mg. per cent. The following day the patient died following a grand mal seizure.

On pathologic examination (Autopsy No. 55A73) the kidneys weighed 120 and 115 gm. There was coarse, grey-yellow surface granulation. The cortex was irregular and thin, with poor demarcation. Microscopic section of the kidney revealed extensive vascular lesions of several sorts. Most conspicuous was necrosis of afferent arterioles and their extensions into segments of the tufts of some of the glomeruli. The landmarks of their walls were obliterated by a fibrillar eosinophilic material that resembled fibrin. At times this material enmeshed red cells. In some of the vessels the coagulum occluded the lumen and infiltrated the

wall. The interlobular arteries and their branches presented sclerotic changes of moderate to marked degree. The intima was thickened by circumferentially laminated fibrous tissue with resultant variable narrowing of the lumen. In many instances basophilic intercellular mucoid material was included in the sclerotic intima. The internal elastic lamella was disrupted, frayed and reduplicated, and the medial coat frequently atrophic. There were small areas of cortical infarction as well as focal necrosis of individual glomeruli. Some of the tubules were slightly dilated and contained cast material. A few of the glomeruli were hyalinized, but there was no conspicuous sclerosis of the viable glomeruli. Areas of arteriolar thrombo-necrosis were found in trachea, pleura, myocardium (dense fibrous tissue with scattered focal hemorrhages), esophagus, stomach and colon.

Summary: Frank scleroderma developed one year before death in a forty-five year old white hypertensive woman. She was admitted to the hospital with blurring of vision and headache of three weeks' duration. She was found to have marked hypertension, retinopathy, cardiac enlargement and scattered pulmonary rales. Anemia, proteinuria and roentgenographic evidence of pulmonary fibrosis were noted. Coincident with brief administration of hydrocortisone and hydralazine there was steady diminution in urinary output and increasing azotemia, culminating in convulsion and death. Examination of the kidneys revealed extensive vascular lesions including necrosis of the afferent arterioles, intimal thickening of the interlobular arteries and small areas of cortical infarction.

CASE VI. A. C., a forty-seven year old white housewife, was first admitted to the Presbyterian Hospital of Pittsburgh (No. D-1851) on October 17, 1954, with the chief complaint of pain in the arm and roughening of the skin. The patient had noted the onset of Raynaud's phenomenon one and one-half years before, soon followed by stiffness and hyperpigmentation of the skin of the fingers and toes. She received "steroids" for an undetermined length of time and was later advised to undergo sympthectomy. There had been a 60 pound weight loss during this illness. There was no history of dysphagia, renal disease or hypertension. Physical examination disclosed normal pulse and temperature and blood pressure of 130/85 mm. Hg. The skin over the extremities was thickened and shiny. The lungs and heart were normal. Flexion deformities were noted in the fingers, elbows and knees. The urine was of specific gravity 1.010 and was free of protein. A few leukocytes were noted in the sediment. The hematocrit was 39 per cent, hemoglobin, 11 gm. per cent and the white blood cell and differential counts were normal. The blood non-protein nitrogen con-

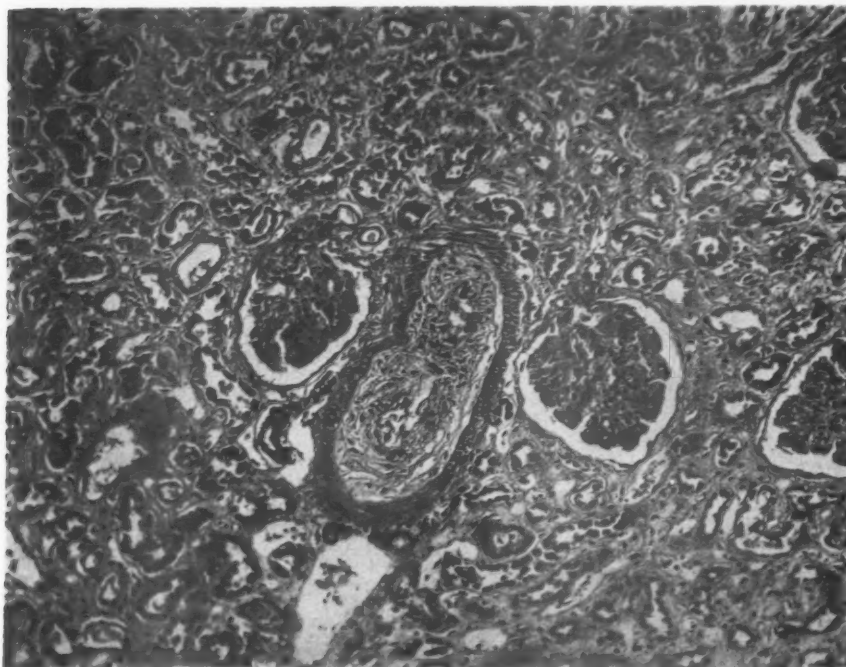


FIG. 6. Case VI. Photomicrograph of interlobular vessel illustrating thickening of intima with narrowing of the lumen. Original magnification, $\times 140$.

centration was 33 mg. per cent. The cardiac contour appeared normal on roentgenographic examination and the electrocardiogram revealed no abnormalities. Esophageal study disclosed minimal cardiospasm. During the first week preceding operation (left thoracic sympathectomy, T₁ to T₆), the patient received 50 mg. of cortisone daily following an initial dose of 300 mg. per day. Following the surgical procedure it was noted that the left arm had become warmer and more freely movable. The blood pressure during the pre-operative period was in the range 118–130/74–94 mm. Hg and postoperatively measured 96–120/64–90. The patient was discharged on November 11, 1954.

She was re-admitted on January 4, 1955 for right thoracic sympathectomy. It was noted that the left hand had continued to improve, with increased warmth and diminished swelling. The patient had begun to experience frequent fronto-occipital headaches and generalized joint aches. Her temperature was again normal and the pulse 80/min. The blood pressure was now 170/110 mm. Hg. The fundi were described as normal. The right arm was swollen and the fingers were cold, pale and sweaty, while the left arm was warm. Two urine examinations were obtained. The specific gravities were 1.005 and 1.015, and protein 1 and 2 plus. The sediment contained many leukocytes. The hematocrit was 33 per cent; hemoglobin, 11 gm. per cent; and white blood cell count 4,000 per cu. mm. with eosinophils 7 per cent. The concentration of blood non-protein nitrogen was 40 mg. per cent. A right-sided sympathectomy (C₇ to T₇) was performed, following which the right arm and hand

became warmer. The blood pressure in the postoperative period ranged around 140/102 mm. Hg. The patient left the hospital on January 16.

A few days later she noted the onset of dyspnea and progressive impairment in visual acuity. A week before her final admission to the hospital (February 3, 1955) the hematocrit was 21 per cent and hemoglobin was 7.7 gm. per cent. The specific gravity of the urine was 1.010 to 1.012, and there was 4 plus protein and an abundance of red cells and broad granular and waxy casts.

On this admission the patient was markedly lethargic. The pulse rate was 90/min. and blood pressure 140/90 mm. Hg. The pupils were dilated and fixed. There was bilateral papilledema and hemorrhages and exudates. Rales were present at both lung bases. The heart was enlarged and there was a soft systolic murmur. There was much muscle twitching. She was given digitalis, parenteral fluids, and 400 mg. of cortisone by intramuscular injection. She died on the second hospital day while undergoing hemodialysis. The concentration of blood non-protein nitrogen had been found to be 211 mg. per cent.

On pathological examination (Autopsy No. A-5523) the right kidney weighed 150 gm., the left 160 gm. The surfaces were pale and coarsely granular with a moderate number of petechial hemorrhages. Microscopic examination disclosed many large subcortical areas of hemorrhagic necrosis. There was intimal proliferation and thickening in the smaller arteries and arterioles with luminal narrowing and areas of acute fibrinoid necrosis. (Figs. 6, 7.) Some of the glomeruli were completely scarred, others were

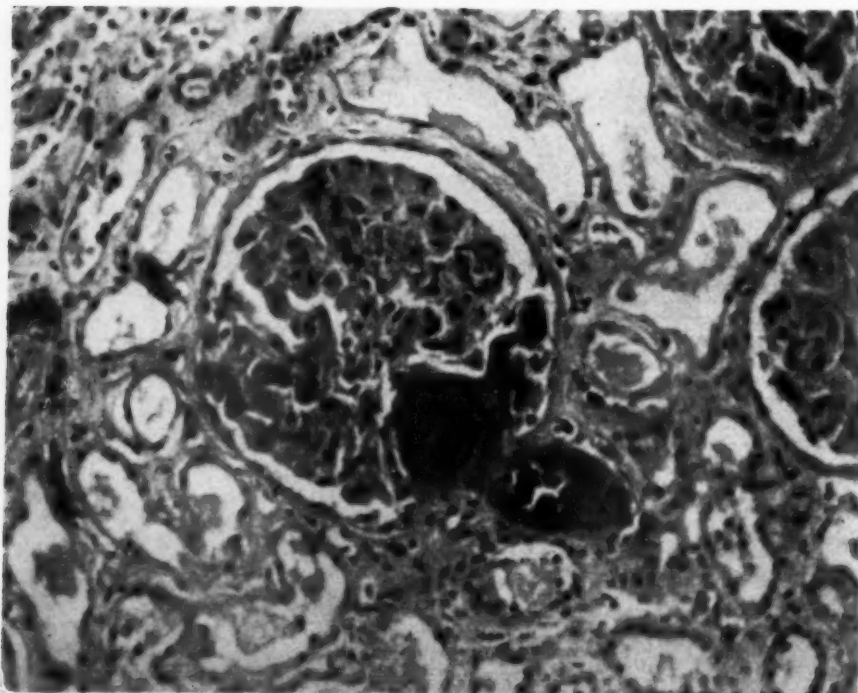


FIG. 7. Case VI. Photomicrograph illustrating fibrinoid necrosis of afferent arteriole extending into glomerular tuft. Original magnification approximately, $\times 200$.

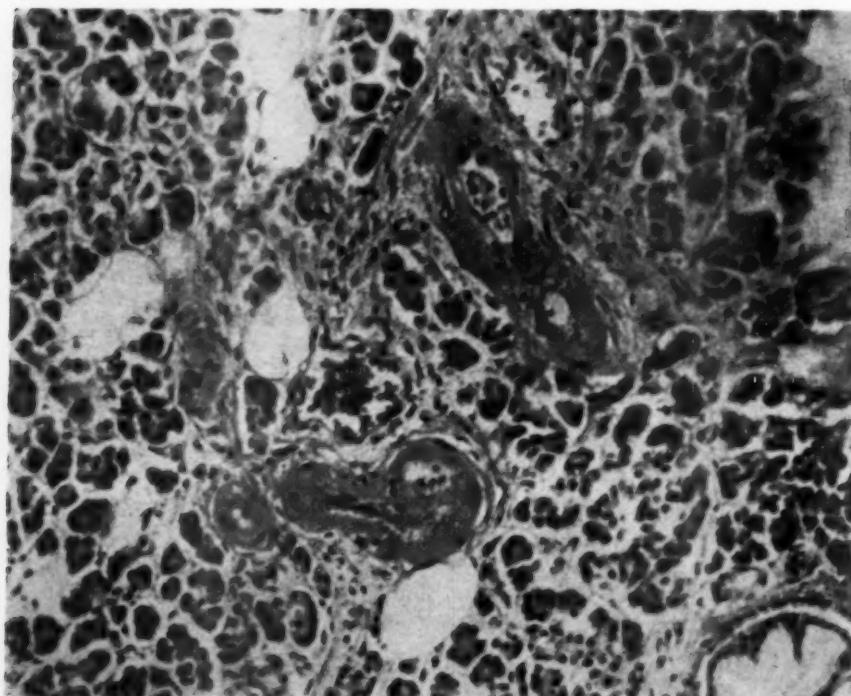


FIG. 8. Case VI. Photomicrograph of pancreas illustrating fibrinoid necrosis involving almost the entire wall of small arteries. Original magnification, $\times 200$.

enlarged and ischemic. Similar vessel changes were noted in the arterioles of the pancreas, spleen, uterus and adrenals. (Fig. 8.)

Summary: Hypertension first developed approximately two months following a left thoracic sympathectomy in a forty-seven year old woman

with scleroderma of one and one-half years' duration. Within a period of another month, during which time contralateral sympathectomy was effected, there was progressive impairment in renal function, the patient dying in uremia. The small vessels of the kidney were found to be

thickened and, in places, necrotic. There were many areas of cortical infarction.

CASE VII. J. P., a forty-three year old white housewife, was admitted to the Presbyterian Hospital of Pittsburgh (No. C.-1937) on November 14, 1952 in a comatose state.

The patient had noted the development of swelling of the feet about a year before admission. This had been followed by swelling, stiffness, and later gradual thickening and hyperpigmentation of the skin of the hands. She had received daily injections of ACTH for a period of two months, after which she experienced a generalized convulsion, and was found to have a blood pressure of 210/110 mm. Hg. There had been no hypertension prior to this time. In the ensuing two weeks the patient had repeated vomiting, progressive oliguria and, after several more convulsions, lapsed into coma. The blood non-protein nitrogen concentration had risen to 228 mg. per cent.

On examination the patient was comatose and tachypneic. The temperature was 102°F., the pulse 122, the blood pressure 160/98 mm. Hg. The skin was taut and thickened and there were numerous acne-form lesions. The face was rounded. The small pupils reacted to light and accommodation. The optic discs were edematous and there were numerous flame-shaped hemorrhages and exudates. The heart was enlarged. The lungs were clear. Loose black bloody stool was present on the bed sheet.

The hemoglobin was 11 gm. per cent, and the white blood cell count 18,500 per cu. mm., 82 per cent of which were neutrophils. The specific gravity of the urine was 1.014, and there was 1 plus protein. There were granular casts and a few white blood cells in the sediment. The urine and blood were sterile to culture. The blood non-protein nitrogen was 196 mg. per cent. The serum albumin level was 2.2 gm. per cent and the globulin was 2.3 gm. per cent.

The patient remained in coma until the time of death on the eighth hospital day. She was given 200 mg. of cortisone daily, by intramuscular injection. Receipt of fluids and hemodialysis with an artificial kidney resulted in some temporary correction of electrolyte imbalance without, however, any concomitant improvement in clinical state. The urinary output fell as low as 88 ml. per day. Frequent liquid stools contained dark red blood. The blood pressure hovered initially around 180/110 mm. Hg, falling terminally to levels as low as 100/60. The patient died on the eighth day, following numerous convulsions. Permission for postmortem examination was not obtained.

Summary: A forty-three year old woman with scleroderma of a year's duration experienced a convulsion after receiving ACTH daily for a period of two months. When hospitalized two weeks later the patient was comatose, and was

found to have hypertension, papilledema, retinopathy, cardiomegaly, melena, proteinuria and marked azotemia. There was continued gastrointestinal bleeding and progressive diminution in renal function, the patient died eight days after admission to the hospital.

CASE VIII. F. G., a fifty year old white female furrier, was admitted to the Presbyterian Hospital of Pittsburgh (No. D-316) on February 18, 1954, with the chief complaint of tightness of the skin of three months' duration.

The patient had first noted swelling of the legs in April, 1953, followed by dryness, hyperpigmentation and thickening of the skin. There was marked tightening of the face, hands arms and legs. Biopsy of skin from the arm in November, 1953 was considered indicative of scleroderma. The patient had received four injections of ACTH and an undetermined amount of cortisone prior to admission. There was no previous history of hypertension or renal disease.

The temperature was normal, the pulse 100, the blood pressure 210/90 mm. Hg. There was marked tightness and hyperpigmentation of the skin. The optic disks were blurred in outline, but no hemorrhages or exudates were noted. The heart was enlarged. There were no murmurs. The lungs were normal. The remainder of the examination was not remarkable save for limitation in extension of the fingers.

The urine contained 2 plus protein and the sediment a few white blood cells. Blood hemoglobin concentration was 9.5 gm. per cent; hematocrit, 36 per cent; and white blood cell count, 14,700 per cu. mm. Of these cells 87 per cent were neutrophils and 13 per cent lymphocytes. The blood non-protein nitrogen level was 104 mg. per cent. A roentgenogram of the chest revealed cardiomegaly and bilateral accentuation of the bronchovascular markings. There was low voltage in the limb leads of the electrocardiogram, and depression of the S-T segment.

On the morning of the third hospital day the patient suddenly became extremely apprehensive. She was found to be gasping and cyanotic, and died soon after. Permission for postmortem examination was not obtained.

Summary: A fifty year old woman with scleroderma of ten months' duration, was found to have hypertension, papilledema, cardiomegaly, anemia, proteinuria and moderate azotemia when hospitalized three days before death. She died soon after the sudden development of respiratory distress.

CASE IX. E. R., a fifty-one year old white female clerical worker, was admitted to the George Washington University Hospital (No. 1-28716) on December 1, 1954 with the chief complaint of headache of three weeks' duration.

The patient first noted stiffness and tightness of the fingers, wrists and forearms in December, 1952. She consulted a physician in March, 1953, who noted that the blood pressure was 140/85 mm. Hg and that the hands were reddened, with early atrophy of the skin. A biopsy specimen was thought to be indicative of scleroderma. There was a faint trace of protein in an uncatheterized urine specimen, which had a specific gravity of 1.025. The patient had noted intermittent headaches over the past one and one-half years, occurring most frequently on arising in the morning. This generalized headache, accompanied by postural vertigo, had become more severe in the three weeks prior to admission. For the past five or six months she had noted a sensation of fullness in the throat as if food were stuck in the chest. This fullness was relieved after belching, but a dull burning sensation persisted. The patient had had pain in the ankles and knees and elbows, lasting one or two days at a time. There was no previous history of kidney disease or of hypertension.

The patient was well developed, well-nourished, alert and cooperative, in moderate distress from headache. The temperature was normal, the pulse 96, respirations 18, blood pressure 224/120 mm. Hg. The skin was tense and shiny over the fingers, hands, wrists and extensor surfaces of the forearms. A small hemorrhage was noted in the right fundus and there was increased light reflex of the arterioles, but no nicking. The lungs were clear. The heart was of normal size and regular in action. There was a soft, blowing systolic murmur heard at the aortic area. At the apex and over the adjacent precordium a short midsystolic murmur was present.

The urine was alkaline, of specific gravity 1.012, and there was a trace of protein. The hemoglobin was 12.7 gm. per cent; hematocrit, 40 per cent; and white blood cell count, 9,100 per cu. mm. (69 per cent neutrophils, 4 per cent bands, 27 per cent lymphocytes). X-ray studies disclosed abnormal activity of the esophagus, manifest by to and fro motion of the barium meal, and there was enlargement of the mucosal folds in the lower esophagus. There was an abnormal small intestinal pattern. Intravenous pyelography was considered normal as were chest films and a barium enema study. Electrocardiogram disclosed a prolonged Q-T interval with low T-waves. At the time of admission the concentration of blood non-protein nitrogen was 32 mg. per cent.

There was some initial improvement in the headache but the patient continued to note a burning sensation in the esophagus. On the twelfth hospital day she became nauseated and began to take very little food. Pentolinium tartrate (ansolysen) was given on the thirteenth hospital day, followed by an abrupt fall in the blood pressure to levels of 140/80 mm. Hg. The patient became dizzy and confused. Nausea and vomiting continued. The abdomen became distended, and bowel sounds hypoactive. On the seventeenth hospital day the patient became disoriented and, acute pul-

monary edema developed, she received aminophylline, mercurial diuretics and morphine. The blood non-protein nitrogen this day was 48 mg. per cent and on the twenty-first hospital day had risen to 138 mg. per cent. The urine now contained 3 plus protein, and there were clumped white cells in the sediment. The patient became comatose, with intermittent singultus and Cheyne-Stokes respiration. The heart enlarged and there was a pericardial friction rub and a diastolic gallop. The patient received hypertonic saline solution but remained in coma with gradually diminishing urinary output. Several daily urine outputs of 300 ml. or less were noted. The concentration of blood non-protein nitrogen rose steadily to a high of 396 mg. per cent, and serum potassium levels to a high of 8.3 mEq./L. The blood pressure, which had fallen to levels of 130-150/70-90 mm. Hg when the patient was receiving pentolinium tartrate (ansolysen), rose to levels of 180-220/90-110 when this medication was discontinued, and remained at these higher levels until shortly before death, when values of 75/40 mm. Hg were recorded. The temperature remained normal throughout until one week prior to death, when it ranged from 38 to 39°C. The patient died on the twenty-ninth hospital day. Permission for postmortem examination was not obtained.

Summary: Severe hypertension with retinopathy and proteinuria approximately seven weeks before death developed in a fifty-one year old woman with progressive systemic sclerosis of two years' duration. Coincident with a sharp reduction in blood pressure following the administration of pentolinium tartrate there ensued a course of rapidly developing cardiac failure, renal insufficiency and death.

SUMMARY OF CASES

There were seven women and two men in this group, ranging from twenty-six to sixty-six years in age. (Table 1.) The duration of symptoms referable to progressive systemic sclerosis in each case totaled three years or less. In addition to diffuse scleroderma, all the patients presented evidence of visceral dysfunction—commonly esophageal and/or cardiac.

In seven patients the terminal illness was heralded by the development of headache and visual disturbances, followed in five by one or more generalized convulsions. In one case proteinuria was the earliest sign of renal disease, and in one patient there was no clinical evidence suggestive of such involvement.

Six patients had in the past received ACTH and/or cortisone, and four of these were taking such medication either at the time of or shortly before the onset of their terminal symptoms.

It is to be noted, however, that three patients had received neither ACTH nor adrenal cortical steroids during the course of their illness.

The clinical findings are given in Table II. All but one patient had marked arterial hypertension. Funduscopic changes included vessel narrowing, hemorrhages, exudates and, in four cases, papilledema. The cardiomegaly which was noted in all patients was accompanied in five by soft apical systolic murmurs. Evidence of pulmonary congestion was present in five patients at the time of their admission to the hospital, and developed in three others shortly thereafter.

Proteinuria was found in eight cases, varying from 1 to 4 plus in qualitative reaction. In two patients in whom a quantitative estimation was made (G. D., J. H.) the protein excretion totaled 0.7 and 1.2 gm./twenty-four hours. Only two urines contained abnormal numbers of red cells, described as "7 to 9 per high power field" in one and "many" in the other. In three instances there were increased numbers of white cells in the urine. A wide variety of casts was present in six of the urines. Red blood cell casts were noted but once.

Estimates of blood urea nitrogen concentration ranged as high as 167 mg. per cent and of non-protein nitrogen as high as 396 mg. per cent. Seven patients died with uremic coma or convulsions in a period of two months or less from the time of recognition of hypertension and/or renal-dysfunction. Postmortem examination was performed in six cases. In five the kidneys were of normal size, in one they were reduced. The organs were pale and the coarsely granular surfaces were dotted with hemorrhagic infarctions. Microscopic examination revealed a characteristic triad of widespread, although focal, vascular lesions. These consisted of (1) intimal thickening of the small interlobular arteries and arterioles (Figs. 5 and 6), (2) fibrinoid necrosis involving the walls of afferent arterioles and glomerular loops (Figs. 1, 3, 5 and 7), and (3) focal cortical infarctions. The renal tubular epithelium was the site of hyaline droplet degeneration. (Fig. 2.) Similar examples of arteriolar thrombocytosis were present in other organs, particularly frequently in the pancreas and adrenals. (Fig. 8.)

COMMENTS

Since Osler noted as early as 1892 that patients with scleroderma were "apt to succumb to

pulmonary complaints or to nephritis" [27], it is surprising that a detailed description of the renal involvement of progressive systemic sclerosis has become available only recently. Despite this belated recognition it appears that renal damage is a common feature of this malady,

TABLE I
COMPOSITION OF PRESENT GROUP OF PATIENTS WITH
PROGRESSIVE SYSTEMIC SCLEROSIS AND RENAL
INVOLVEMENT

Case	Age (yr.) and Sex	Duration of Illness (yr.)	Organ Involvement	Previous Therapy
I, C. F.	66, M	3½ mo.	Skin, esophagus, muscle, kidney*	Adrenal cortical extract (terminally)
II, V. M.	44, F	8 mo.	Skin, esophagus, muscle, lung, synovium, kidney*	ACTH, hydrocortisone, cortisone (terminally)
III, M. B.	26, F	3	Skin, lung, heart, kidney*	Adrenal cortical extract, thyroid extract, cortisone
IV, G. D.	50, M	2	Skin, heart, kidney*	Phenylbutazone, cervical sympathectomy
V, J. H.	45, F	1	Skin, heart, esophagus, kidney*	Cortisone, hydrocortisone
VI, A. C.	47, F	2	Skin, heart, kidney*	Cortisone, dorsal sympathectomy
VII, J. P.	43, F	1	Skin, heart, kidney	Cortisone (terminally)
VIII, F. G.	50, F	10 mo.	Skin, heart, kidney	ACTH, cortisone
IX, E. R.	51, F	2	Skin, esophagus, heart, kidney

* Postmortem examination performed.

lesions similar to those just described having been reported in a great number of the cases of progressive systemic sclerosis coming to post-mortem examination [2,6-9,11,13-19,22-32].

The evidence of renal involvement in these patients ordinarily appears late in the course of illness and constitutes an ominous prognostic sign. The clinical findings have varied from minimal proteinuria [27], through partial renal insufficiency [6,9,26] to complete renal failure and death in uremia [13,14,24,25,29-32].

It is not uncommon to find marked renal lesions even in those patients who present little or no evidence of renal dysfunction before death. Thus Talbott et al. [23] noted extensive renal endarteritis with focal cortical necrosis in a young woman with a normal blood non-protein nitrogen level on the day of death. Mathison and Palmer [27] found "wire loop" glomerular lesions and infarctions in a woman with scleroderma dying in congestive heart failure with normal

TABLE II
CLINICAL FEATURES IN PRESENT SERIES OF CASES OF PROGRESSIVE SYSTEMIC SCLEROSIS WITH
RENAL INVOLVEMENT

Patient	Duration of Terminal Illness (wk.)*	Blood Pressure (mm. Hg)	Funduscopy Findings	Urinary Findings				Terminal Concentration of Blood Non-protein Nitrogen (N.P.N.) or Blood Urea Nitrogen (B.U.N.) (mg. %)	Anti-hypertensive Medication
				Protein	Red Blood Cells (per high power field)	White Blood Cells (per high power field)	Casts		
I, C. F.	1	210/110	Vessel narrowing, exudates	2	Rare	1	Many granular	180 (N.P.N.)
II, V. M.	†	132/74	Normal	0	Occasional	41 (B.U.N.)
III, M. B.	2½	250/140	Vessel narrowing, exudates	4	7-9	3-5	Granular	141 (B.U.N.)	Hydralazine, alkavervir
IV, G. D.	3½	220/120	Vessel narrowing, hemorrhages, exudates	1-3	Occasional	Occasional	Granular hyaline red cell	105 (B.U.N.)	Cryptenamine, pentolinium tartrate, reserpine, alkavervir
V, J. H.	3-4	180/110	Vessel narrowing, papilledema, hemorrhages, exudates	1-3	6-20	Granular hyaline renal failure	167 (B.U.N.)	Pentolinium tartrate, hydralazine
VI, A. C.	4	170/110	Papilledema, hemorrhages, exudates	2-4	Few—very many	Few—clumps	Many granular and waxy, few hyaline	211 (N.P.N.)	(Hemodialysis)
VII, J. P.	3	160/98	Papilledema, hemorrhages, exudates	1	Few	Granular	260 (N.P.N.)	(Hemodialysis)
VIII, F. G.	3 days	210/90	Blurring of disk margins	2	Few	104 (N.P.N.)	Phenobarbital
IX, E. R.	7	224/120	Vessel narrowing, hemorrhages	Trace 3	Clumps	396 (N.P.N.)	Pentolinium tartrate

* From time of recognition of hypertension and/or renal dysfunction to death.

† Neither hypertension nor evidence of renal dysfunction developed.

blood pressure and non-protein nitrogen and but a "trace" of protein in the urine. Similarly the second case described by Bevans [9], a fifty-six year old man with cutaneous, esophageal and cardiopulmonary disease, was found to have fibrinoid necrosis involving the wall of practically every medium-sized and small renal artery. Yet urine examination one week prior to the patient's sudden death was normal and the blood urea nitrogen was 43 mg. per cent. In case V. M., herein reported, although the urine remained free of protein and with high specific gravity to the time of exodus, striking lesions were noted in the renal vessels.

Several observers have commented, in cases such as these, upon the relative paucity of clinical abnormalities compared to the impressive pathologic alterations. Part of the explanation for this apparent disparity may lie in the rapidity of progression of the renal lesions so that the period

in which the clinical evidence of renal disease can be observed is limited. Then, too, although the renal lesions are widespread, they are predominantly focal in distribution, so that the patient may die from other complications without the development of renal insufficiency.

In those patients in whom frank evidence of renal insufficiency does develop the course is one of relentlessly progressive hypertension characterized by marked retinopathy, cardiac failure, convulsions, profound oliguria and uremia. The first symptoms may be those of headache and/or blurring of vision (J. H., E. R.). In other cases (M. B., G. D.) convulsive seizures have heralded renal involvement.

The urinary abnormalities in our group of cases are similar to those previously reported. These findings include moderate proteinuria, small to moderate numbers of red cells, white cells, and casts of various description, most

commonly granular and hyaline. Red cell casts were noted in one of our cases (G. D.). The urine of another (J. H.) contained the "granular motility cells" ("glittering leucocytes") considered by Sternheimer and Malbin [20] to be highly suggestive of pyelonephritis but this diagnosis was not substantiated at the postmortem examination.

Various reports have suggested that the development of renal lesions may have been related to treatment with ACTH or cortisone [15-18]. We would note, however, that there are numerous reports describing such renal involvement in patients receiving neither of these agents [2,6,9,11,13,21-30,32-34]. Indeed many of these cases antedate the steroid era. In the series presently described two patients (G. D., E. R.) had had no steroid therapy, one patient (C. F.) received adrenal cortical extract only as a terminal procedure, and in another (M. B.) cortisone was given for only a short time and discontinued more than a year and a half before the onset of her final illness. In two of these cases (J. H., J. P.), however, and in two instances previously cited [15,16] the very dramatic onset of cardiovascular-renal complications in a period of but days to weeks following the initial administration of ACTH (or cortisone) does suggest some causal relationship. The patient reported by Lunseth et al. [15] became violently ill after receiving 475 mg. of ACTH over a period of four days, anuria developed and he died three days later following a convulsion. The pathologic findings were those of severe fibrinoid necrosis involving glomerular loops, afferent arterioles and interlobular arteries, with "no evidence of previous vascular or glomerular involvement." Similar vascular fibrinoid necrosis was present in several other organs, including testes, esophagus, stomach and lungs. The patient observed by Sharnoff et al. [16] was a woman who had been receiving 100 to 125 mg. of cortisone daily for a period of approximately two months when this medication was discontinued and ACTH given for two days, only to be stopped when increasing hypertension and edema were noted. Within four days marked hypertension, papilledema and uremia developed, and several days later the patient died. There was intimal fibrosis and obliteration of the lumina of interlobular arteries as well as small areas of wedge-shaped infarctions of the cortex. In contrast, the cases reported by Beigelman et al. [6], Bagnall and Robinson [17] and Bartels et al. [18] first

displayed evidence of kidney damage months after the institution of ACTH, and the renal vascular lesions were those of intimal hyperplasia and fibrosis with cortical infarctions, suggesting a more chronic disturbance of renal vessels. It is not clear, therefore, whether ACTH actually induced the development of renal damage or merely accelerated the progression of already existing lesions.

The development of hypertension and nephrosclerosis in the rat given various anterior pituitary preparations or desoxycorticosterone acetate is well documented [35] and evidence of a permissive action of the adrenal cortical steroids upon vasoconstriction by nor-epinephrine has been described [36].

In the patient with already existing renal disease sufficient to produce azotemia, the catabolic action of the adrenal steroids complicates the problem by increasing the nitrogen and potassium loads presented to the failing nephrons. In such a case rising concentrations of blood non-protein or urea nitrogen may reflect this increased catabolism, rather than indicating increasing renal failure.

The patients herein reported received a variety of antihypertensive drugs in the course of their final illness. These included such agents as pentolinium tartrate (ansolysen), hydralazine (apresoline), alkavervir (veriloid) and cryptenamine (unitensen). In at least three instances (M. B., E. R., G. D.) it appears that these drugs were of but little value, and indeed may have hastened the progression of renal failure. The adverse effects of periods of shock in patients M. B. and C. F. suggest that in these cases there was further damage to kidneys incapable of adjusting to sudden alterations in systemic blood pressure [37]. The predilection of the pathologic changes for the interlobular and afferent arteriolar vessels suggests that the internal renal vascular resistance may be relatively fixed in these kidneys. Dilatation of other vascular beds (for example, splanchnic) by antihypertensive drugs might therefore serve only to shunt blood away from an already ischemic kidney. Undue preoccupation with the systemic blood pressure may represent a dangerously misplaced emphasis. A coincidentally affected myocardium may fail to respond to drug-induced hypotension with a rise in cardiac output, and further aggravate the situation.

The pathologic alterations in the kidneys center in the small arteries of the renal cortex

and vary considerably in severity. Although widespread, the lesions tend to be focal in distribution. Interlobular arteries, afferent arterioles and glomerular capillaries may all be affected. The individual lesions appear variously acute and chronic. The former consist of a segmental necrosis of the intima with intraluminal and intramural deposition of compact fibrillar and hyaline eosinophilic material (fibrinoid). Little or no associated inflammatory exudate is found. The more chronic alterations are those of intimal thickening with cellular fibrous tissue, described by some as mucoid [13] or myxomatous [23] in appearance. The vessel lumina are markedly narrowed and frequently completely occluded. The focal cortical infarctions associated with these vascular changes are a conspicuous feature of the pathologic process. A variety of lesions in the tubules have been described. Klemperer has noted the frequency of hyaline droplet changes in the lining cells of the proximal convolutions [38]. There may be tubular dilatation with proteinaceous material in the lumina as well as areas of tubule atrophy.

Moore and Sheehan [13] believe that the initial lesion is intimal thickening of the intralobular vessels occurring probably but a few weeks before death, followed by ischemia and atrophy of the cortex, and then fibrinoid necrosis of the distal part of the intralobular vessels and afferent arterioles which results in renal failure. They believe these lesions to be distinguishable from those of malignant hypertension but their statement that "most cases of scleroderma with (marked) renal lesions do not have significant hypertension" appears to be incorrect [6,16,24,31,32].

Sokoloff [39] is of the opinion that the fibrinoid lesions are indistinguishable from those of acute malignant hypertension of other origin and that the older sclerotic lesions resemble those of the usual long-standing essential hypertension. He has suggested that these latter lesions in the interlobular vessels may represent the healing or organization of past necrosis and thrombosis or a response to a more insidious, non-necrotizing vascular damage. It is of interest to note that these proliferative lesions were found in the one patient of our series (V. M.) who remained normotensive throughout her illness, indicating that these lesions are not the result of hypertension *per se*. Perhaps these lesions are an end-result of localized abnormal vasomotor activity in the small renal vessels, similar in nature to the Ray-

naud's phenomenon which is so common in the patient with progressive systemic sclerosis. Examination of the digital arteries of such patients has revealed marked intimal proliferation with almost complete obliteration of the lumens [2,24]. It is possible that the fibrinoid necrosis seen in other viscera besides the kidney then results from systemic hypertension developing shortly, perhaps only hours to days, before death.

Klemperer [38] has postulated that both the fibrinoid alteration in the arteriolar walls and the hyaline droplet degeneration in the tubules may result from the transudation of an abnormal protein from the blood ("paraproteinemia") and/or urine ("paraproteinuria"). He believes that "the fibrinoid alteration seen in scleroderma gains in significance because it reflects a chemical abnormality of the amorphous ground substance which has been regarded as the extracellular amorphous matrix from which (collagen) fibers may originate. The fibrinoid substance shows some unique tinctorial features which suggest its transformation into a substance with staining qualities similar to those of collagen." While moderate, and at times even marked hyperglobulinemia is of frequent occurrence in progressive systemic sclerosis [40], this thesis is only speculative at this time.

In the cases herein presented the fibrinoid material appears to have consisted at least in part of a variety of hematic elements, including fibrin. (Fig. 4.) This fibrinoid accordingly differs from that found in the kidney of patients with systemic lupus erythematosus. In the latter the material consists predominantly of a more homogeneous degraded nucleoprotein [41] which Gueft and Laufer believe provoked a non-specific inflammatory reaction and exudation of fibrin. Several observers have noted "wire loop" lesions of the glomeruli in progressive systemic sclerosis, and have held these to be indistinguishable from those occurring in lupus [9,25,27], but the former have not been associated with "hematoxylin bodies." The renal involvement in lupus has been described as beginning with a focal glomerulitis characterized by focal hypercellularity and occasional fibrinoid changes. This progresses to diffuse glomerulitis, thickening of the basement membrane, "wire loop" changes and glomerulonephritis with epithelial crescents [42]. Afferent arteriolar involvement is infrequent in lupus as compared to progressive systemic sclerosis. Sokoloff [39]

has pointed out that there are no nephritic components to the scleroderma lesion, and he is impressed by the different discrete appearance of the capillary thrombus in lupus, that is the thrombus typically has less intimate continuity with the walls than it does in scleroderma.

Also to be differentiated among the "collagen diseases" are the renal lesions of so-called malignant rheumatoid arthritis. In one case Bevans and co-workers [43] described granulomas in which the primary lesion appeared to be that of fibrinoid necrosis of the wall of small blood vessels. In others a non-specific type of interstitial scarring or infiltration has been found. The lesion described in some cases of rheumatic fever [44] consists of interstitial deposits of lymphocytes, plasma cells, some polymorphonuclear leukocytes, and indefinitely outlined cells with pale nuclei in the adventitia of smaller arteries and arterioles. The intima is usually unaffected by the process. Blaisdell noted that these alterations were seldom sufficient to produce clinical renal disease.

Lastly, two less usual examples of renal lesions should be mentioned. Horn [45] reported extensive calcium deposition in the loops of Henle in a patient classified as having poikilodermatomyositis; the description of this case is suggestive of progressive systemic sclerosis with calcinosis. One patient with scleroderma described by Swarm and Germuth [14] was found to have granulomatous lesions about and involving the arteries within the kidney and liver which were considered compatible with periarteritis nodosa. There had been no symptoms suggestive of renal disease in this case.

SUMMARY

Renal involvement is of frequent occurrence in the natural course of progressive systemic sclerosis. The present report describes the clinical and pathologic features of this complication in a group of nine patients, seven of whom died in uremia.

The lesions are focal and consist of intimal sclerosis and hyperplasia involving primarily the interlobular arteries, together with fibrinoid necrosis of the walls of afferent arterioles and glomerular loops. When extensive, these vascular changes lead to widespread focal cortical infarction. The clinical findings are those of abrupt cardiovascular renal disease characterized by severe hypertension, retinopathy, cardiac failure, convulsions and rapidly progressive renal

insufficiency. When the lesions develop relatively early in the course of the patient's illness renal dysfunction dominates the clinical picture to the exclusion of the other visceral manifestations previously described.

The injudicious use of various hypertensive drugs in these patients may possibly aggravate existing kidney damage and hasten the development of renal insufficiency.

The origin of the renal lesions of progressive systemic sclerosis and their differentiation from those of the other diseases of collagen is discussed. It is suggested that the intimal hyperplasia of the interlobular arteries may result from abnormal spasm of these vessels. This in turn may lead to systemic hypertension and, terminally, fibrinoid necrosis of the arterioles of the kidney and other viscera. It is not yet clear whether administration of ACTH or adrenal cortical steroids may induce these renal changes or merely accelerate the progression of already existing lesions.

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ADDENDUM

The case study of "true scleroderma kidney" by Calvert and Owen (*Lancet*, 271: 19, 1956) was noted after completion of the present report. These authors note that mild renal involvement was suspected in their patient when the blood urea level was normal and before cortisone treatment was begun. Histologic studies revealed the characteristic vascular lesions but evidence of other visceral involvement was not found.

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Seminar on Atherosclerosis

The Epidemiology of Coronary Heart Disease

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THE increasing prominence of coronary heart disease (CHD), especially in the Western world, has led to a preoccupation of medical scientists with study of the causation of this disease. While there is still more discussion than research, the problem is unusually complicated. Of the triad of experimental approaches—clinical, laboratory and epidemiologic—it appears that the last may be particularly appropriate for this problem.

The proportion of the recorded death rate caused by heart disease in the United States has increased from about 9 per cent in 1900 to almost 40 per cent in 1956 [7]. As we shall see, such statements tend by oversimplification to exaggerate and distort the problem because the changes of age composition of the population, the increase of precision of diagnosis and cause of death certification, and the elimination of other causes of death which were formerly manifest in young people have all tended to exaggerate the increase of CHD as a cause of death. Nevertheless, every practicing physician must be impressed with the frequency of CHD in his experience. These circumstances prompt us to examine two questions: Has there been a real increase in mortality from CHD in the past twenty years? Has the "progress" which man has made in altering his environment inadvertently introduced or exaggerated the agents which cause CHD?

The examination of such questions and their ramifications is the function of the science of epidemiology. At best, we can hope by such a method to identify and to measure the force of the agents which contribute to cause. The proof of identity and the application of information in prevention and cure are the functions of the laboratory and clinical methods of research.

The fundamental procedure in the epidemiologic method—as in other scientific disciplines—

is an orderly examination of hypothesis. The individuality of the method rests particularly in the use of special skills and models for sampling populations, in the systematic classification of measurements and in the application of appropriate statistical procedure to interpretation of the data. The epidemiologist is apt to be especially skillful at formulating hypotheses. It is axiomatic that one must ask the right question to get the proper answer. Epidemiologists are concerned with the identity of the circumstances which influence the pattern of a disease in a population. The interest, then, is in the factors of time, place and person.

The science of epidemiology had its beginning with John Graunt, a London merchant who undertook to interpret the city's Bills of Mortality in 1662. These were the weekly records of deaths which were begun in 1592 during one of the plague epidemics. After 1603, burials, christenings and plague deaths were recorded. At first intermittent, these tables were expanded to include surrounding areas and by 1629 included records of deaths by sex and cause. Graunt's description [2] of how these data were collected is of interest because then as now mortality data, which are an important material of the epidemiologic method, are subject to serious limitations of accuracy.*

"When anyone dies, then either by tolling, or ringing of a Bell, or by bespeaking of a Grave of the Sexton, the same is known to the Searchers, corresponding with the said Sexton. The Searchers hereupon (who are antient Matrons, sworn to their Office) repair to the place, where the dead Corps lies, and by view of the same, and by other enquiries they examine by what Disease or Casualty the Corps died. Hereupon

* Graunt's classic ("Natural and Political Observations Mentioned in a following Index and made upon the Bills of Mortality. With reference to the Government, Religion, Trade, Growth, Ayre, Diseases, and the several Changes of the said City" London 1662) has been partially reproduced in *The World of Mathematics Vol. III*, p. 1420 ff. J. R. Newman published by Simon & Schuster, New York, 1956.

they make their Report to the Parish clerk” Beginning with Graunt, epidemiologists have necessarily been cautious fellows. Again from Graunt “So that, this casualty being so uncertain, I shall not force myself to make any inference from the numbers, and proportions we find in our Bills concerning it [refer-

TABLE I
NUMBER OF DEATH CERTIFICATES (FOR APPROPRIATE
UNITED STATES REGISTRATION AREAS) WITH HEART
DISEASE ENTERED AS A DIAGNOSIS [4]

	1917	1925	1936	1940
Heart disease:				
Primary cause . . .	128,719	191,226	341,350	385,191
Secondary cause . .	46,067	81,513	103,448	112,505
Ratio of all certifi- cates with heart disease listed to those with heart disease listed as primary cause . . .	1.36	1.43	1.31	1.29

ring to a specific cause of death]—for there is much difference in computing the number of Lunatics that die and those that die by reason of their Madness.” Nevertheless, Graunt was able to draw many useful conclusions from his study of the Bills of Mortality. Out of his work have come three areas of activity: life assurance (Graunt constructed a crude life table), the theory of probability and the science of vital statistics. One hundred fifty years elapsed before William Farr established the orderly collection and tabulation of British vital statistics. Greenwood has observed [3] “Farr found medical statistics in such a state that only men of genius, like Graunt, could use them—when Farr retired any reasonably intelligent man could draw accurate conclusions from them.”

At the first International Statistical Congress held in Brussels in 1853 Farr and d’Esperance submitted a proposal for a list of cause of death, the first step toward international comparability of mortality experience. This list was repeatedly revised and in 1893 Bertillon’s International List of Causes of Death (ILCD) was adopted. The ILCD has since been revised at ten year intervals. These revisions have tended to expand causes as medical perception and technics have developed. A continuing and involved problem is the assignment of death with multiple causes. Until 1949 the ILCD was used in conjunction with an arbitrary Manual of Joint Causes. This, by definition, assigned the primary cause of death. The procedure was unpopular with physicians and was abandoned with the sixth revision of the ILCD made in 1949 and the physician has since been asked to assign the prime cause. The important fact is that while the ILCD has contributed to the conformity of certification neces-

sary for epidemiologic utility, the problem is not solved and there are serious irregularities in time series of mortality by cause as well as among different regions and principalities. Indeed it is apparent that both physicians and medical examiners must differ profoundly in their assignment of cause of death. Woolsey and Moriyama [4] have shown an example of the potential extent of tabulation distortion of heart disease in United States death certificates. (Table I.) Gover [5] has also considered the effects of the death certificate requirement of assignment of a primary and contributory causes of death. Heart disease ranked first in 1940 (United States) both as a primary and as a contributory cause. Since less than half the death certificates filed report only a single cause of death it is apparent that the physician filing the certificate can greatly influence death by cause rates according to the way he selects the *primary* cause. Death certification is thus exceptionally sensitive to medical thought and fashion. One can see that an “epidemic” could be self-perpetuating. This possibility became especially probable in 1949 when use of the mandatory Manual of Joint Causes was abandoned.

The uncertainty of demographic data, which are the materials of epidemiology, is increased by their large volume and tabular orderliness, which may be deceptive. Caution and skepticism is the necessary characteristic of an epidemiologist. Morris has aptly observed [6] “it was not the vital statistician, epidemiologist or social medicine workers in general who first engaged in these exercises, (epidemiology of CHD) and their hesitation was only partly due to their well known indolence.” At the same time it is apparent that the interpretation of demographic data which are accurate and competent requires only logic and common sense. The epidemiologist is then a skeptical philosopher dealing with the products of diagnosticians and vital statisticians. It is surprising they are so few!

Before turning to our questions certain definitions are necessary. The term coronary heart disease will refer to disease of the heart caused by limitation of blood supply to the myocardium resulting from disease of the coronary arteries. This definition is very similar to that for ischemic heart disease proposed for international use by the Study Group on Atherosclerosis and Ischaemic Heart Disease of the World Health Organization [7]. While ischemic heart disease may have some semantic distinction the advantage of common usage will probably preserve coronary heart disease until an accurate etiologic classification is possible. The latter term has no serious disadvantages. Coronary heart disease must include some instances not caused by atherosclerosis of the coronary arteries but these are presumed rare and not a cause of

important error. CHD is primarily a clinical diagnosis and comprises angina pectoris, which is a highly uncertain and subjective diagnosis, myocardial infarction, coronary occlusion (i.e. death with coronary artery lesions but without signs of infarction) and myocardial fibrosis not attributable to causes other than chronic myocardial ischemia. The latter is generally an anatomic diagnosis. A variable proportion of these clinical diagnoses (ranging from 8 to 50 per cent in the most favorable circumstances in the United States and in Great Britain) [8] are investigated by autopsy. An important proportion of the deaths assigned to CHD are sudden deaths which are assigned to this cause with a bare minimum of medico-legal investigation and are presumed to be CHD because they occur suddenly. Morris and Heady found in their retrospective study of insured British physicians [9] that 24 per cent of the initial manifestations of CHD among men forty to sixty-four years of age were sudden death. In the Framingham study [10] thirteen of forty-three men in whom "heart attacks" occurred during a four-year period of observation were affected with "sudden death." The investigation of these deaths is generally limited. In the Commonwealth of Massachusetts in 1954 [11] 24.2 per cent of all deaths were medical examiner cases. About one-fifth of the medical examiner's cases were ascribed to violence, one-tenth were preparatory for cremation, and in only 5.7 per cent of all the medical examiner's cases were autopsies performed. The autopsy rate in Suffolk County (which includes Boston) was 19.4 per cent of all medical examiner cases. The important point is that almost one-third of the cases of CHD may end with sudden death, that these cases will be studied only by the medical examiner, and that in only a small proportion will autopsies be performed.

The reliability of the assignment of clinical cause of death was studied at the Los Angeles County General Hospital in the period from 1933 to 1937 [12]. Retrospective investigation of about 8,000 routine autopsies, 38 per cent of which were performed upon patients dying within forty-eight hours of hospitalization, indicated the proportion of correct clinical diagnoses shown in Table II. It is pertinent that only 50 per cent of the clinical diagnoses were confirmed for patients who died within forty-eight hours after admission to the hospital. James, Patton and Heslin [13] examined the same question in 1,889 deaths in which autopsies

were performed in the Albany, New York area during 1951 and 1952. The inconsistencies between death certificate and autopsy data led the authors to doubt that death certificate data are a valid basis for epidemiologic studies of many chronic diseases, including arteriosclerotic

TABLE II
PER CENT OF CLINICAL DIAGNOSES CONFIRMED BY AUTOPSY
(LOS ANGELES COUNTY GENERAL HOSPITAL 1933 TO
1937 [12]) STILLBIRTHS AND CORONERS' CASES
EXCLUDED

Cause of Death	Per cent Confirmed
All causes	79
Measles	100
Cancer of the breast	97
Other and unspecified heart disease	83
Cerebral embolism and thrombosis	76
Cerebral hemorrhage	74
Arteriosclerosis	66
Diseases of coronary arteries	66
Lobar pneumonia	64
Softening of the brain	16

heart disease. For the latter cause only about 73 per cent agreement was obtained for the two methods of classifying cause. General arteriosclerosis was underestimated on the original death certificates and hypertensive heart disease was overestimated. On the other hand, a large proportion of CHD is diagnosed with the aid of electrocardiographic evidence. This is objective and almost always unequivocal. Without this evidence it is doubtful that epidemiologic analysis could be applied to heart disease vital statistics. It is unfortunate that many population studies of CHD, especially when carried out in medically undeveloped areas, have not made better use of this most decisive evidence of the existence of the disease.

Secular Changes of Mortality Assigned to CHD.

Are we in the midst of an epidemic of CHD? The evidence that bears on this question deserves careful examination because it may reveal the causal factors of CHD. It is also important that the facts be clarified before an aversive campaign of fund raising and publicity seeking is sanctioned by the scientific community.

The trend of mortality in the United States for several pertinent causes in white men forty-five to fifty-four years of age for the registration area

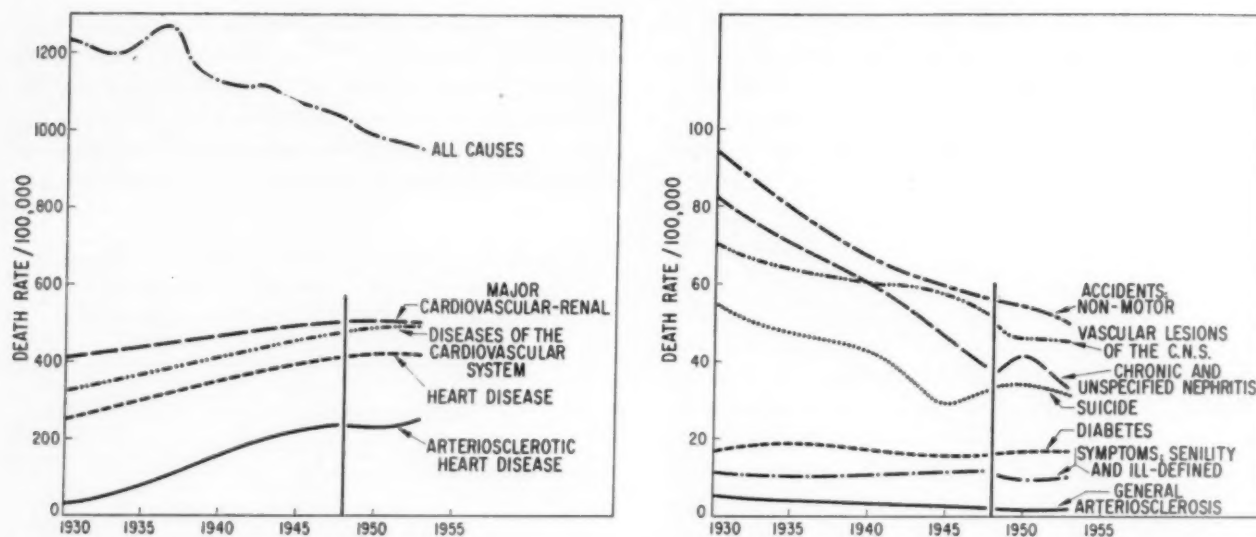


FIG. 1. Trends of death rates for several causes—United States, white men aged forty-five to fifty-four. The vertical line at the end of 1948 indicates the change from the use of the fifth to the sixth revision of the International List of Causes of Death. The data for 1949 and following years have been adjusted with the comparability ratios described by the National Office of Vital Statistics (see text and [79]). The data for arteriosclerotic heart disease (420) assume a comparability ratio of 1.30.

is shown in Figure 1. Nine Western and Southern States have entered the death registration area since 1924, and the area was completed in 1933 with the entry of Texas.

The data for white men aged forty-five to fifty-four years are shown for several practical reasons. Consideration of a narrow age band minimizes the otherwise important effects of changing age composition of the population. Moriyama and Gover [15] have illustrated the important effect of age changes in the population both on the crude death rate and especially upon the mortality rate attributed to cardiovascular disease. Consideration of white men forty-five to fifty-four years of age includes the middle decade of high susceptibility to CHD and it avoids some of the complexities of multiple disease which are more prevalent in death after age fifty-five. Woolsey and Moriyama [4] concluded that the trend of heart disease mortality in the interval from 1900 to 1930 could not be evaluated because the death registration area of the United States was being enlarged and the population at risk was being increased by additions of young populations with limited medical facilities. All these factors obscure the true course of events. After 1930 the death rate assigned to heart disease was found to be definitely increased for every age group over forty-five years. But Woolsey and Moriyama observed a compensating decrease in the death rate for this age from a group of causes of death which

are clinically closely associated with heart disease. For example, deaths assigned to intracranial lesions of vascular origin, chronic nephritis, arteriosclerosis and high blood pressure were all diminished after 1930 as mortality assigned to heart disease increased. This balancing effect was sufficient to remove all signs of an upward trend when the entire class of heart disease and these related causes were combined. These effects are illustrated in Figure 1.

The adoption of the sixth revision of the ILCD in 1949 resulted in an important change of certification of deaths, largely caused by abandoning the Manual of Joint Causes but also caused by regrouping of some titles. The National Office of Vital Statistics arranged for the deaths in 1950 to be coded according to both the fifth and sixth revision methods. A 10 per cent sample of these data illustrating the comparability of the data has been published [74] so that the comparability rates (sixth/fifth) can be used to adjust the data for 1949 and thereafter to values that would have been obtained with the fifth revision. Woolsey and Moriyama were cautious in interpreting these data (to 1945) and they did not venture an opinion about the true course of heart disease mortality. However, as early as 1932 Bolduan and Bolduan [76] had concluded from data obtained in New York City that the rise of heart disease mortality was fictitious. It seemed then that deaths assigned to heart disease were rising in the face of a

steady decline of age-specific death rates for all causes of death. This suggested to them that the increase of heart disease was caused by changing practices of assignment of cause of death.

Cohn and Lingg [17] begin their discussion of the changes of mortality assigned to diseases of the heart, kidneys and blood vessels with the remark that this—of all the cause-specific mortality—was the most difficult to comprehend. They review the persuasive evidence that the net change of death rates for cardiac, vascular and renal diseases combined is very slight in the interval from 1900 to 1940 and that the divergent courses of rates for individual entities is the result of changing practices of diagnosis and certification. They also show a graphic kind of cohort analysis. While it has become conventional to consider mortality by age at some specific time, the difficulty arises that each age group represents a different group of persons with quite different backgrounds of biologic experience. Suppose instead the mortality experience of groups (cohorts) defined by a birth date range are followed at successive ages. This treatment might be expected to reveal either the appearance or the fluctuations of a mortality force by the resulting changes in the successive cohort mortalities [18]. This method has been notably successful in the demonstration of a real increase in cancer mortality [19,20]. The data for heart disease are not as satisfactory for this analysis because of changing diagnosis especially. Cohn and Lingg found no striking increase in heart disease mortality through 1940 although a definite upward trend for successive cohorts was present. This kind of trend is to be contrasted with the more dramatic changes revealed for tuberculosis.

The mortality data for selected causes summarized by the National Office of Vital Statistics [14] permits an examination of the problem of changing certification practices as a cause of apparent change of mortality forces. If we examine a plot of the death rates for *all causes* with time for white men aged forty-five to fifty-four years, we observe that since 1935 there has been a steady decline of rates through 1953. (Fig. 1.) This decline represents a complex average of many individual causes which show quite different trends. Our problem is that of determining whether or not some of the opposite trends are the result of "transference" of deaths among categories. Suppose we select those causes of death which meet the following

a priori criteria: (1) fatal diseases which by the terminal circumstances may often cause physicians to differ in their assignment to causation either because of uncertainty of diagnosis or for reasons of social stigma cast upon the family or perhaps for other reasons of convenience; (2) fatal diseases for which treatment since 1935 has not been notably effective either in preventing or delaying such deaths. With these conditions we are prepared to assume that the true mortality for these causes has been essentially unchanged since 1935 and that the apparent changes represent reassignment of these deaths to CHD for reasons of current interest, conformity and colloquial practice.

We can then compute the sum of the annual deviations of the mortality for each disease from that observed in 1935—an arbitrary starting point. It is selected because it would seem to have allowed time for the dissemination of knowledge about CHD and yet permit a sufficiently long span of data to show trends. Will the net change among these "transferable" diseases account for the observed change of mortality assigned to CHD?

The first criticism that will be raised will concern the acceptability of the transferable diseases. The seven entities selected are as follows:

1. Vascular lesions of the central nervous system. This represents a clinical entity often characterized by "sudden death," thus minimizing clinical studies which would permit an accurate diagnosis. Some of these deaths may in fact be due to arterial emboli from the endocardium subsequent to myocardial infarction. Deaths attributed to this cause have diminished steadily over the past thirty years even though no medical progress can claim credit for this. The trend would seem to represent changing diagnostic practice and the diminution of deaths assigned here would seem largely to have resulted from assignment to CHD.

2. Chronic nephritis and nephrosclerosis. This is another category of arteriosclerotic disease which is often characterized by hypertension and sudden death in congestive failure. Persons dying with uremia are assigned to senility, symptoms and other causes. There was no effective treatment to account for the apparent diminution in mortality.

3. Diabetes is commonly terminated with heart disease. Insulin has been widely available since 1935 and while death from diabetic coma

occurs there is no reason to believe its frequency should have changed greatly. Aside from diabetic coma the other fatal mechanisms in diabetes have not been changed by medical treatments.

4. Suicide is an important cause of death and

TABLE III
THE POTENTIAL MAGNITUDE OF "TRANSFERENCE" OF CAUSE
OF DEATH FROM SEVEN EASILY MISTAKEN CATEGORIES
OF CAUSE TO DISEASE OF THE CORONARY ARTERIES
(Rates/100,000 for United States white men forty-five to
fifty-four years of age. See text for terminology.)

Year	Observed Death Rate	"Transference"	Predicted Rate
1935	65
1940	168	27	141
1945	215	67	148
1950	248*	88	160
1953	252*	102	150

* A comparability ratio of 1.3 has been assumed.

one which is especially liable to occur under circumstances which obscure accurate reporting of the true cause. While a death by gunshot or hanging can scarcely be mistaken, the other common methods with poisons are often not readily apparent. A person previously well and found dead is likely to be assumed dead of heart disease. Perhaps more important are the social stigmas of suicide which induce the persons concerned to conceal the true cause in favor of some socially acceptable cause—of which CHD is the most useful. While suicides have regularly diminished during war time—and this is reflected in the figure for the interval from 1940 to 1945—the over-all trend since 1935 has been downward. This downward trend of suicide mortality is suspect because the United States population has increased and suicides are closely related to population density. Few would contend that medical progress has been made in preventing suicides [27].

5, 6. Senility and general arteriosclerosis are almost trivial causes of death in the age range forty-five to fifty-four but they are included because they represent a "crude" diagnosis which might, in better circumstances of medical care, have been called CHD.

7. Accidents, non-motor vehicular, are, like suicides, a likely concealment for sudden death caused by CHD. Motor vehicle accidents are

excluded because these may have been expected to change with drastically changing motoring conditions. While the safety promotion groups may demur, there is little reason to believe that accident mortality should have changed since 1925, and yet it has steadily decreased.

The time span 1935 to 1953 covers three revisions of the International Nomenclature of Disease. Revision IV was used during the years 1930 to 1938, revision V from 1939 to 1948, and revision VI in 1949 and thereafter. The National Office of Vital Statistics finds little effect for these causes of death in the transfer from revision IV to V [14]. The change to revision VI in 1949 caused major aberrations for certain causes which have been adjusted with the comparability ratios already described. Use of age-restricted groups also minimizes the potential error because comparability ratios are often age- and sex-dependent.

Such an analysis gives the results shown in Table III. The increase of coronary disease can be accounted for by the decreases in these seven categories of disease. Which is more plausible, that CHD has increased almost four-fold since 1935 or that these seven causes of death—for which we have little or no effective prevention—have been diminished on "the books" by transfer to the CHD category? Such evidence cannot be decisive but it strongly suggests that CHD mortality has not increased.

In addition to the influences discussed which affect time trends of heart disease mortality there is another and more subtle phenomenon which epidemiologists refer to as the effect of competing causes of death. Cornfield [22] has recently discussed the theoretic aspects of this effect. Even though, *biologically speaking*, co-existing diseases are not independent in their effects they tend to be made so by the artefact of our certification of cause of death which requires one prime cause. Competing causes of death interfere with one another in two distinct ways. In Cornfield's terminology (1) they interfere in a *formal sense* because an organism dead of cause A is no longer liable to cause B. Thus the effect of A is to diminish the effect of B. Men dead of tuberculosis at age twenty-five are no longer at risk of dying of CHD. (2) In an *empirical sense* the animals dying early of cause A may have had a different susceptibility to cause B than do the survivors with which the lethality of B is judged. We can never know the lethality of B totally free of the effect of A, particularly if the interval of development of

B is long. Here, then, is a complication in the study of chronic disease because competing causes are usual. It can be shown that removal of the competing causes which precede the disease in question have the effect of "uncovering" this disease. It then assumes a prominence not caused by an increase of its lethality.

Goldberg et al. [23] examined the question of the effects of deaths from non-cancer causes on the probability of developing cancer.* Using life table methods they showed that the changing morbidity assigned to cancer in New York State is not due solely to changing forces of cancer but is strongly increased by the "uncovering" effect of non-cancer mortality. This effect varies with cancer by site, and for some sites the apparent increase was in fact a decrease in the interval studied (1943 to 1950), when the adjustment for other causes of mortality had been made. A similar analysis of heart disease mortality should be made. The removal of earlier causes of death would be expected to account for a part of the apparent increase of CHD.

We are left with the empiric effect of competing causes and there seems to be no solution available for its measurement. Does, for example, an influenza epidemic leave a group as susceptible to CHD as was that which it killed? Are the men who survive a war as susceptible to CHD as those who were killed? This general question was an interest of Pearson [24] who took the position, now often discounted, that lowering mortality rates at early ages must inevitably produce higher mortality rates at later ages because the force of natural selection was thus delayed. For the present problem we have no information on the importance of this "generation effect."

The effects of World War II on the mortality experience of selected European countries has been widely used as evidence of the importance of environment—and particularly of the diet—upon mortality forces. It must be recognized that the civil commotion of war brings an additional hazard to accurate and complete diagnosis and certification of fatal diseases. This would seem to be an inappropriate time for studies of trends of mortality. Morris [6] has discussed the uncertainty of attributing the observed changes of mortality during World War II as observed in

* More precisely, the probability of being reported to the New York State Health Department as having cancer.

several European countries to associated specific environmental changes. It has been contended that the diminution of mortality in Great Britain, Norway, Sweden, Holland, Finland and parts of Russia was the consequence of a reduction of fat intake [25]. Morris challenges this as an over simple tale. He states that the mortality from CHD in Denmark was only half that in Finland, Canada and New Zealand. The mortality assigned to CHD in Stockholm was only half that attributed in Edinburgh, Aberdeen, Newcastle and Cardiff, and yet the fat intakes in all these places are believed to be high. Furthermore, there is a disturbing lack of synchronism of events. The British mortality began to rise again in 1943 although dietary restrictions remained until 1947. Strøm has reviewed the Norwegian experience [26a,26b]. From 1941 through 1945, several population studies in Norway indicated a profound decrease of both meat and dairy products in the dietary with a concomitant increase of cereal, vegetable and fish products. However the problem was complex because conditions changed from month to month and persons of different areas and occupations were able to secure supplementary foods with different degrees of success. Such estimates of food intake were then applied to the interpretation of mortality data for the entire country. In the period from 1940 to 1944 there was an increase in mortality from all causes apparently related to the increase of infectious disease in subjects under the age of twenty and to the increase of violent deaths among adult men. The Norwegians had begun the use of the ILCD (v) in 1941. Death rates from "circulatory diseases" † diminished in the interval from 1939 to 1945 and then rose, but in 1949 had not yet reached pre-war levels. The mortality rates for men and women were roughly parallel. There was no evidence that this decline was caused by reassignment from mortality previously attributed to senility since this also declined. There was an important increase of deaths assigned to unknown or ill-defined causes but Strøm believed this was not important. If the mortality for circulatory disease in the period from 1938 to 1940 equalled 100, the proportionate rate for 1944 and 1945 was 78 and for 1948 and 1949 it was 91. If the combined mortality for circulatory and unknown or ill-defined causes in the period from 1938 to 1940 equalled 100, in 1944 and

† Including "apoplexy," chronic nephritis and senile gangrene.

1945, this was 91 and in 1948 and 1949 it was 97. Two other circulatory phenomena were observed to parallel these mortality changes. The mean of measured blood pressures fell and the frequency of postoperative embolic and thrombotic diseases fell. Strøm believed that these phenomena were related to the dietary changes. Dedichen [27] believed that the effect of the war on circulatory diseases was real and mediated through an effect of the diet upon the clotting mechanism of the blood. The difficulty with this experience in Norway, as with that in Holland and in Finland, is not so much an acceptance of the demonstration that a real diminution of CHD occurred but rather in the uncertainty of assigning the cause. The data will permit several attractive "causal" agents. The affected peoples were working harder, smoking less and, in general, either losing weight or gaining less than in pre-war conditions. Nor is circulatory disease the only change of health status measurable. Among the Norwegians, in addition to more infectious disease and violent deaths, mental disease developed in fewer persons and there were lower mortality rates for diabetes, tuberculosis and malignant tumors. Children had less dental caries, and maternal mortality was less. Can dietary changes account for all this? In particular, can dietary fat changes explain these changes in the burden of disease? I think not.

Malmros [28] has discussed the unique change in the disease sequelae of World War II. Unlike previous wars, no epidemic of infection accompanied the turmoil but rather a kind of respite among the "chronic" diseases. Malmros indicated that this wartime influence of environment upon heart disease mortality was a useful alternative to the impracticable method of comparing national experiences. He discussed the experience in Sweden, Finland, Norway and Denmark, and compared this with the United States. He concluded that the decline in cardiovascular disease in the first three countries during the war was associated with a reduced consumption of eggs, butter and other foods rich in cholesterol. This association was most marked for the urban population, he believed, because they could supplement their dietaries but little. Denmark failed to show a wartime decrease of arteriosclerosis mortality, because (so Malmros believes) there was no decrease of butter and egg consumption even though the total fat intake decreased by one-third. The lack of a latency period between dietary changes and mortality

changes was a cause for comment by Malmros. He suggested that atherogenesis was potentially a rapid process and that "placques may grow in a comparatively short time and perhaps after only a few months produce serious local disturbances."

Ryle and Russell [29] have published an especially searching study of the natural history of coronary heart disease as revealed in the statistical reports of the British Registrar-General through 1945. They emphasize the increase of CHD and although they admit the importance of clerical transference in this increase they agree with the Registrar-General's 1938 opinion that transfer of assignment of cause could account for "only a fraction" of the recorded increase. The objection to this explanation is that only the most obvious sources of transfer, namely vascular and "other heart" disease, were considered. As we have observed (*vide supra*) the problem of transference is more subtle than this because many other causes of death may be, and no doubt are, either transferred to CHD by the certifying physician or elevated to the prime cause. Ryle and Russell then observe that in the interval from 1938 to 1945 the trend of CHD in England and Wales changed because "diseases of the coronary arteries increased precipitously at the same time that diseases of the myocardium were diminishing." They admit that this is probably a reflection of changing certification practice rather than a change of disease behavior. The similarity of these rate changes for different ages and for men and women supports this explanation. Ryle and Russell then compute an extrapolated "expected death rate" for coronary and myocardial disease by computing the rate which would have resulted had the 1931 to 1939 rate of increase of these diseases continued through 1945. The results indicate that the "expected rates" exceeded the observed rates by 5 to 30 per cent for men. They conclude that CHD was in fact increasing less rapidly in the period from 1939 to 1945. It would have been as reasonable to conclude that the transference phenomenon was diminishing with increasing dissemination of knowledge about CHD. Additional evidence for a certification artefact rather than a biologic effect is the similarity of the sex ratio of the mortalities for the two causes. For coronary disease at age fifty-five to fifty-nine the ratio M/F was about 4 in the interval from 1921 to 1943 and for myocardial disease the ratio was about 1.45.

Lew [30] has taken the position that the increase of CHD in the United States since 1940 has been relatively small and not justification for the public alarm which has been created. Lew has shown a figure illustrating the trend of CHD mortality in the period from 1940 to 1955 for all persons; this figure has been age adjusted and also has been corrected for ILCD differences by reclassifying the fifth revision data according to sixth revision methods. The trends are constantly upward but they are small and Lew believes these represent changing practices in certification. He has shown that while there has been an increase of CHD (including angina pectoris) mortality between 1940 and 1955 there has been a larger decrease of mortality assigned to other cardiovascular-renal disease. This is reasonably explained as a change of assignment of cause of death. Lew's evidence for changing practices in certification is derived from the regional differences of cause of death in the United States. Generally speaking, the more rural and medically isolated regions have shown the greatest increases of mortality attributed to CHD in the interval from 1940 to 1948 and conversely the environs of urban medical centers have shown the least increase. Lew seems to see in this a wave of professional sophistication rather than true regional differences. The sophistry has also affected the medical examiners and coroners, since in New York City a third to a half of the deaths assigned to CHD were certified by the medical examiners in November 1956. Lew believes that about one-third of the apparent increase of CHD mortality since 1940 is attributable to this new knowledge and fashion in diagnosis and certification. He believes that this effect, the changes of age composition, and the broader limits of disease called CHD account for more than 85 per cent of the increase in death rate assigned to CHD.

It is also instructive to consider a kind of clinical evidence which is often brought to bear on the question but which is not helpful, because it lacks the essential qualifications of description of population and criteria of diagnosis; it is, in short, the "clinical impression." Cassidy [37] believes that coronary disease has increased in prevalence in England since 1920 to 1925 and he bases this belief on his experience with his own practice, reinforced with the redoubtable opinions of Osler and Mackenzie for an earlier period. Such expressions of experience generalized to "fact" have had a profound effect upon

progress in medicine and not always a salutary one.

Regional Differences in CHD Mortality. The description of the behavior of a disease with respect to occurrence in time and place is basic to the epidemiologic method. One of the earliest demonstrations of vital statistics was the higher death rate among city dwellers. William Farr proposed that the healthiest districts of England be the yardstick of public health efficiency. Although this disadvantage of urban life has been repeatedly observed both for all causes and for many specific causes of death it has never been adequately explained. In the era of the infectious diseases it was often tacitly assumed that the concentration of persons in urban areas facilitated the transfer of the causal agent. The demonstration that such a chronic disease as CHD also shows a higher rate of mortality in urban places introduces a new problem in the explanation of mechanism.

There are certain complications in mortality statistics arranged by place. Census data, which are the indispensable denominators in death rates, are tabulations of persons by legal residence, i.e., *de jure*. Nevertheless, medical centers do attract the sick and crippled to their environs, just as salubrious climates tend to attract the aged and infirm. These factors distort mortality by place tabulations.

The tabulation of mortality by place was begun in the United States in 1914. In subsequent years reporting of cause of death by place has been extended until in 1950 mortality tabulations by county were obtained. Dorn [32] has discussed the opportunities offered by these data, but little use has been made of them for heart disease.

Another nemesis returns to confound cause of death by place. The different nations and areas within the United States have wide differences in the proportion of death certificates with multiple causes listed, one of which must be assigned the prime cause. These differences range from 1.2 per cent of certificates with multiple causes in Greece in 1936 to 59.6 per cent in the United States in the same year; and from 40.2 per cent in the East South Atlantic region of the United States in 1940 to 63.1 per cent in New England in 1940 [33].

Enterline and Stewart [34] have described the geographic pattern of CHD* in the United

* Coronary heart disease is used as the equivalent of ILCD VI "arteriosclerotic heart disease."

TABLE IV
RAW MATERIAL FOR EPIDEMIOLOGIC THEORIZING
(Death rates/100,000, all ages, both sexes)

Nation	Year	All Causes	Arterio-sclerotic Heart Diseases 420-22 *	Other Diseases of Heart 430-34 *	Senility, Ill-defined and Unknown 780-95 *	Food "Available" per Capita per Day				
						Year	Cal-ories	Fat (gm.)	Protein	
									Ani-mal (gm.)	Vege-table (gm.)
Australia †	1953	910	241	23.9	17.5	1951-1952	3290	122	63	32
Austria	1954	1215	195	59.6	85.8	1951-1952	2660	44	36	42
Canada	1954	821	223	12.3	12.4	1951-1952	3007	124	54	36
Denmark	1954	905	202	35.2	15.3	1951-1952	3225	140	51	40
Ireland	1953	1175	275	40.7	143.9	1951	3480	118	49	48
New Zealand	1953	884	252	27.5	6.2	1951	3380	102	69	33
Sweden	1953	970	230	35.2	51.7	1951-1952	3090	127	59	34
Switzerland	1953	1019	238	19.9	95.0	1951-1952	3180	114	52	44
Scotland	1954	1198	337	23.6	31.9	1951-1952 ‡	3080	123	43	42
England and Wales	1953	1142	298	17.1	17.3					
N. Ireland	1954	1090	289	38.4	60.8	1952	3117	135	61	29
United States	1953	959	282	14.0	13.7					
Belgium	1953	1206	112	141.3	170.3	1951-1952 §	2930	110	39	46
Luxemburg	1954	1136	198	100.0	88.2					
Ceylon	1954	1035	25	14.5	198	1952	1880	11	10	36
Chile	1953	1264	36	90.8	104	1951	2340	48	47	48
Egypt	1952	2024	28	13.6	293	1951-1952	2360	35	11	59
Italy	1953	1003	176	13.6	83.9	1951-1952	2510	57	21	58
Japan	1953	891	45	16.3	102	1951-1952	2130	17	12	46
Netherlands	1953	768	147	18.4	39.6	1951-1952	2835	109	40	40
Norway	1953	846	135	32.1	68.0	1951-1952	3060	125	54	43
Union South Africa	1951	880	163	15.0	32.0	1952	2705	60	26	48
West Germany	1953	1101	163	93.7	1952	2765	101	37	39

NOTE: Adapted from United Nations Demographic Year Book and Tables of Food Supplies Available for Human Consumption [38,39].

* ILCD rubrics.

† Excludes aborigines.

‡ United Kingdom data.

§ Economic Union data.

States as revealed by the vital statistics of 1950. After age adjustment, they observed a two-fold difference in CHD death rates for white men between states with low rates such as New Mexico and Arkansas, and states with high rates such as New York and Rhode Island. The differences between areas for white women showed a similar pattern but were somewhat larger. There was a tendency for the states with high death rates attributed to CHD to cluster and these areas centered about the conurbations associated with New York City, Chicago, New Orleans and Los Angeles. The finding conforms with the earlier experience that death rates for

CHD are higher in urban areas [35]. Enterline and Stewart proposed no specific explanation although they were persuaded that the regional differences were real. Lew [30] has made the ingenious explanation already described, namely that the regional differences are largely a reflection of different degrees of medical sophistication in certification of cause of death. Lew illustrates a strong association of age-adjusted death rate attributed to arteriosclerotic heart disease and the number of internists per 100,000 white persons. The fact that the CHD death rates and the death rates from all causes are closely associated, and further that the excess of

TABLE V
DEATH RATES/100,000 BY CAUSE—MEN FORTY-FIVE TO FIFTY-FOUR YEARS OF AGE

Cause of Death	ILCD Rubrics	U. S. White 1950	U. S. Japanese 1949-1952	Hawaiian-Japanese 1949-1951	Japanese 1952
All causes		984.5	711.5	695.8	894.8
Arteriosclerotic heart disease	420-422	348.5	152.5	88.8	40.9
Vascular lesions of the central nervous system	330-334	53.7	54.7	64.2	129.1

NOTE: Adapted from Gordon's sources [47] and the United Nations Demographic Yearbook 1954 [39].

CHD deaths will largely account for the excess of total deaths is probably the best evidence that the force of CHD mortality is truly larger in the urban areas. But unresolved is the question: Does urban life select persons with heart disease—or does it cause heart disease?

The British experience with regional differences in mortality also indicates important differences among areas. Men in rural areas have a measurably lower death rate than women in rural areas [36]. For coronary disease mortality the rural advantage is about 15 per cent for men and 10 per cent for women for all of England and Wales.

The question of international differences of CHD is almost as controversial—and unscientific—as international diplomacy. The collection of comparable vital statistical data has just begun. There is a notable parallelism between the social and economic development of a nation and the quality of its vital statistics. It is, on the surface, an attractive proposal that we may find the clue to causation in CHD by comparing people with different environmental characteristics. The difficulty arises, assuming that adequate measurements have been made, that the cultural attributes are so multiple and devious that one cannot safely assign the cause of the measured differences. Mainland has succinctly put this problem "However desirable a piece of epidemiologic information may be, we may have to recognize that it is not merely difficult or expensive, but actually impossible to obtain. Unless thorough and prolonged thought and detailed planning give reasonable assurance of success, it is better to refrain from a survey than to produce equivocal results which not only waste effort and money but bring epidemiologic methods into disrepute" [37].

It is a popular but not very profitable game to select nations whose vital statistics show differ-

ent death rates attributed to "heart disease" or even to CHD and then to search for associations among other available population data. The search has generally been among the Food and Agricultural Organizations Food Balance tables [38]. The vital statistics are readily available in the Demographic Year Books of the World Health Organization [39]. An example of the material is shown in Table IV. While the vital statistics may be sound for local use it seems unsafe to compare them among nations. Many nutritionists experienced with dietary histories doubt that food balance sheets have meaning in evaluating the food intakes of individuals. And if we face these obstacles and find an association of diet and disease how do we interpret its meaning?

A unique example of international comparisons of vital statistics may be found in the mortality experience of Japanese in the United States, Hawaii and Japan. It has been stated that autopsy and clinical experience in Hawaii revealed less arteriosclerosis and heart disease among Japanese than among Caucasian residents [40]. Gordon [47] has examined the material of the National Office of Vital Statistics supplemented with Japanese data. He found that Japanese men thirty-five to seventy-four years of age have lower death rates for diseases of the heart than do white American men of these ages. The death rates among Japanese men for diseases of the heart are low in the United States (compared to white men), still lower in Hawaii, and much lower in Japan. (Table V.) The excess of deaths for vascular lesions of the central nervous system is important among the Japanese in Japan and the excess is greater among women and above age fifty-four. Gordon tended to interpret these geographic differences of mortality among Japanese as an expression of some cultural or environmental effect upon the

biological forces of mortality. This is a hazardous conclusion until an examination of the identity of medical diagnostic practices in the three cultural groups has been established. Gordon has commented upon the large fluctuation of death rates for vascular lesions of the central nervous

TABLE VI
STANDARDIZED MORTALITY RATIOS BY SOCIAL CLASS
(ENGLAND AND WALES) MEN

Cause of Death	Social Class				
	I	II	III	IV	V
(1930-1932) Thirty-five to Sixty-four Years of Age					
Coronary heart disease	237	148	95	66	67
Myocardial degeneration	77	92	94	105	122
(1950-1952) Twenty to Sixty-four Years of Age					
Coronary heart disease	150	110	104	79	89
Myocardial degeneration	67	82	97	98	137

NOTE: Adapted from Table v. The Registrar-General's Decennial Supplement, England and Wales 1951. Occupational Mortality I. London, HMS. O., 1954.

system among the Japanese in Japan since 1918. This diagnosis seems to be an uncertain one. If, indeed, the prevalence of this disorder is as high in Japan as the mortality data suggest, one would expect to find a large number of persons who survived the attack with neurologic disease. This finding has not been documented. Nevertheless, few would doubt that Gordon's data demonstrate some excess of heart disease in white men and probably an excess for this cause among Japanese-American men when they are compared with men in Japan. If we accept this qualitative difference in the groups how are we to use the information? To be useful, the environmental factors which cause this difference must be identified.

The Effects of Activity Differences on CHD. There is a widespread conviction among doctors that CHD is a particular hazard to professional and business men. Morris et al. [9] have confirmed the frequency of CHD in a large group of British physicians thirty-five to sixty-four years of age who were insured with non-cancellable policies and could thus be traced through company records. The

usual explanation for this proclivity was amusingly described by Arnott as the "stress and strain" theory [42]. To quote him: "The ready acceptance of the 'stress and strain' concept is very understandable. It nourishes the *amour propre* of the believer and it is readily acceptable to the unfortunate victim and his relatives. It places ischemic heart disease in the position of being the unjust reward of virtue. How much nicer it is when stricken with a coronary thrombosis to be told it is all due to hard work, laudable ambition and selfless devotion to duty—than to be told it is due to gluttony and physical indolence." It has proved difficult to resolve the importance of these antithetical causes because stress and strain, physical activity and gluttony are each exceptionally difficult to measure. A useful beginning has been made by Morris and his colleagues with the data for mortality by occupation of the British Registrar-General [43]. The hypothesis is well stated there " . . . that men in physically active jobs have a lower incidence of coronary heart disease in middle age, than men in physically inactive jobs." Percy Stocks in 1951 had described [44] the regular trends of CHD observed in the mortality by occupation data from 1930 to 1932. The favorably placed social classes* have coronary artery disease, the less well placed classes have myocardial degeneration. (Table vi.)

An index of mortality called the standardized mortality ratio (SMR) is the usual British way of stating such mortality comparisons. This is the ratio of the actual to the "expected" deaths, ex-

* The British Registrar-General has, since 1912, grouped occupations into social classes for reporting occupational mortality. In 1912 eight social classes were distinguished. Since 1921, five social classes have been used. This is not a classification of individuals but rather of occupations. Economic status is only incidentally reflected in the classification. The five social classes and the percentage distribution of occupied and retired men in 1951 are as follows:

Class	Description of Occupations	Per cent of All Occupied and Retired Men
I	Major professions	3.4
II	Small business and other professions	15.2
III	Skilled workers, blackcoated, etc.	51.9
IV	Semi-skilled and agricultural	15.7
V	Unskilled, most laborers	12.3

pressed as a percentage. The expected deaths are the deaths obtained by applying the age-specific rates for men of all occupations to the number of men in the specific occupation being examined. If the SMR for an occupation is 200 for a given cause it means that this occupation has twice the death rate of the entire population, which includes all occupations. Stocks proposed that differences of expenditure of energy would explain these occupational differences just as well as "anxiety." Morris and Heady [43] analyzed the data for the occupational mortality from 1930 to 1932 published in the British Registrar-General's Decennial Supplement. The physical activity of about two and a half million men of seventy occupational groups in social classes III, IV and V combined were classified into three categories of work which were "heavy," "intermediate and doubtful" and "light." The mortality from CHD for men in the heavy working category aged forty-five to sixty-four years was about one-half that of the men in the "light" working category. The heavy workers experienced more fatal accidents but this was the only cause of death for which they were at disadvantage. There was a variety of diseases with little or no association between mortality and work load category, including valvular heart disease, vascular lesions of the central nervous system, nephritis and bronchitis. Certain diseases showed a definite increasing trend of mortality from heavy to light work, irrespective of the social class, and this trend persisted among several occupational groups. The data for men aged forty-five to fifty-four years for several causes are shown in Table VII. Morris and Heady discuss the complication that results in such an analysis if men do light work because of disease and do not, as the hypothesis proposes, develop the disease because of light work. The artefact of disease determining the work seemed unlikely for the first group of diseases in Table VII because of the usual manifestations and courses of the diseases. The distinct trend for diabetes may represent confusion of prime cause of death in certification since diabetes on the death certificate often means dying with diabetes but of another cause.

In another place Morris considers the Registrar General's data on the occupational mortality from 1949 to 1953 which centers on the British census of 1951 [45]. Such analyses depend upon a census and one was not made in 1941. The available data are preliminary and are

based on a 1 per cent sample of the 1951 census data. The mortality from CHD by social class in England and Wales (1950) was illustrated in Table VI. Morris discusses these associations with great caution. There seem to him to be signs of "new diseases" such as CHD which are

TABLE VII
MORTALITY IN LIGHT WORKERS AND IN HEAVY WORKERS
(ENGLAND AND WALES 1930-1932 FOR SOCIAL
CLASSES III, IV AND V COMBINED)
(Men forty-five to fifty-four years of age. Average death
rates per million)

Cause of Death	Heavy Work	Inter-mediate Work	Light Work
Coronary heart disease	139	225	337
Cancer of lung and pleura . .	96	158	157
Disease of prostate	26	28	31
Appendicitis	77	83	116
Diabetes	77	84	89
Duodenal ulcer	82	137	163
Cirrhosis of liver	47	59	58

NOTE: Adapted from Table III [43].

waxing and "old diseases" such as tuberculosis which are waning. The first tend to affect the rich and the second the poor. Morris lists six possible hypotheses which may explain the behavior of CHD:

1. A high fat dietary causes CHD.
2. Exercise protects against CHD.
3. Smoking causes CHD.
4. Alcohol protects against CHD.
5. Nervous strain causes CHD.
6. Obesity causes CHD.

But Morris has not yet proposed that young men become lean, hard-working, hard-drinking, vegetarian farmers who never smoke and never worry. No doubt there are many men who would question the advantage of this regimen even if we could assure the result.

The data on occupational mortality for Scotland have been briefly reviewed with respect to CHD and diseases of the respiratory system by Morrison [46]. Using procedures similar to those previously used by Morris and Heady [43] for the data of England and Wales, Morrison finds an impressive excess of mortality for CHD among social classes I and II. The occupations classified as "light work" tended to have standardized mortality ratios for CHD of 130 or more and the

occupations classified as "heavy work" showed ratios of 60 or less. Morrison commented that these findings support three of Morris' hypotheses, viz., the effects of inactivity, a fat diet and excessive nervous strain. Since the dietary habits of the population have not been adequately measured and the "nervous strain" is probably not measurable, the exercise hypothesis would seem to be presently the most amenable. Garry et al. [47], with data on a small number of people for dietary intake and energy expenditures, found the following:

Social Class	Total Calories				Fat per Day (gm.)	Calories as Fat (%)
	per Day	At Work	At Leisure	During Sleep		
Miners IIIA...	3660	1750	1420	490	150	33.5
Clerks IIIB...	2800	890	1410	500	119	35.3

But the SMR for miners (all types) from 1950 to 1952 was 96 and for clerks it was 138 [46], for coal miners in England and Wales the SMR is 78. The difference here seems to be exercise not dietary fat.

Lilienfeld [66] has examined the relation of socio-economic status to heart disease mortality in the Baltimore, Maryland experience of 1949 through 1951. Lacking a classification according to occupation Lilienfeld used the data of census tracts in which were recorded, for 1950, the proportion of home ownership, the median monthly rentals and the general kind of occupation of household heads. Using this kind of information he divided the city's population into five classes. In contrast to the British findings—and it should be observed that the British Social Classes and Lilienfeld's classification by census tract data have no clear equivalence—the mortality in Baltimore assigned to coronary heart disease showed no trend among classes. Death rates attributed to myocardial degeneration were highest among the low socio-economic classes in Baltimore with evidence of a distinct trend. The latter cause resembled the British experience but combining the two causes for Baltimore data left the low economic class with the highest death rate from these causes whereas a similar combination of British data still leaves the Social Class I (professional people) with the

highest death rate. These differences seem to indicate that biological forces should not be implicated as the explanation of the mortality differences until the equivalence of classification of economic classes and medical procedures has been established.

Morris and Raffle [48] have described an ingenious study of the role of occupation upon the incidence and clinical manifestations of CHD among employees of a London transport company. The health records of 25,000 male employees, aged thirty-five to sixty-four years, were examined. In the initial two years of the study there were 111 first "attacks" of CHD. The attack rate was 2.7 per 1,000 for 15,500 drivers and 2.0 per 1,000 for 9,500 conductors who spent their work day walking up and down the aisles and stairs of the buses. The disease was manifested differently in the drivers for in only 13 per cent of them did the disease begin with angina pectoris although 38 per cent of the CHD in conductors began with this manifestation. The mortality rate in the first three days for the drivers was about double that for the conductors and the mortality rate at three months was 1.3 and 0.6 per 1,000, respectively, for drivers and conductors. The authors interpreted this as suggesting that the greater physical activity of the conductors protected them and also led to more angina pectoris rather than to myocardial infarction or coronary occlusion. It may be, however, that occupation selection will explain the transport workers experience and the die was cast for CHD by events that preceded the men's employment. As Dr. Howard Sprague has eloquently expressed it. "The men who develop heart disease may just be the kind of people who like to be on the head end of a bus." Morris did find in a subsequent investigation [49] that the transport company's records of sizes of uniforms issued indicated that the sedentary drivers were larger—and presumably fatter—men when they started their employment than were the conductors. Furthermore, conductors who became drivers were also larger men than the other conductors.

Sex Differences in CHD Mortality. One of the striking epidemiologic features of CHD is the difference of its behavior among men and women. All types of study, whether clinical, autopsy, retrospective or prospective, have observed that under fifty years of age the disease selects men and after this period the ratio male/female begins to diminish. Any tenable theory

of the causation of CHD must explain this sex selection. It seems established that early oophorectomy diminishes the protection of women both to atherogenesis [50] and to the development of CHD [51]. Reference has been made to the advantage, among urban dwellers, which women have for mortality from CHD [36]. The British occupational mortality also showed a distinctly lower SMR for the married women (classified by husband's occupation) of social classes I and II than were found for men in these classes. These comparisons must eliminate diagnostic and certification differences so that the difference is probably real. Indeed, clinicians will scarcely require persuasion on this point for CHD in a woman under fifty years of age and without diabetes, hypertension or hypercholesteremia is very rare.

Madigan [52] has studied the extent of environmental influences upon the favorable mortality circumstances of women. He studied a carefully selected sample of male and female members of religious orders who live in unusually constant and comparable environments. His findings indicated that biologic factors were more important than cultural in affecting mortality. Thus it was nature not nurture which had the predominant effect.

The extent of the predominance of CHD in men has been vehemently discussed. Keys has proposed [53] that the sex ratio of CHD (male/female) is related to the total level of CHD mortality. When the force of CHD mortality becomes high the ratio falls because the protection of "female" is overwhelmed. Lee and Thomas [54] observed that the ratio is also very low when the force of CHD or atherogenesis is very low. Walker, Anderson and Bersohn [55] found a sex ratio approaching 1 in their Bantu material. It is pertinent that Lober [56], who used perhaps as efficient a system of grading atherosclerosis as has been developed, found that the anatomic evidence showed a much lower sex ratio in his Minnesota autopsy material than those usually found for CHD. These initial studies of the sex selection of CHD seem to emphasize the need for more intensive study of this phenomenon. The disparity of the sex ratio for atherosclerosis compared with CHD, the suggestive sensitivity of the sex ratio to the force of CHD mortality, and this excellent opportunity in vital statistical data to eliminate the complexities of diagnostic and certification differences among different areas, all offer unique

opportunities for study. The similarity of dietary habits and the dissimilarity of physical activity among husbands and wives during their reproductive period affords another promising opportunity to study the role of these hypothetical factors.

The Anatomic Evidence. The debate is sometimes confused by the addition of anatomic data because CHD, the clinical entity, is not equivalent to atherosclerosis, the anatomic entity. Very little can be concluded from the spate of anatomic data concerning the prevalence of atherosclerosis of the coronary arteries. Hospital autopsy series tend to be "selected" in a complicated way whether in areas that are medically highly developed or in primitive areas. In addition, no satisfactory method has been found for evaluating the extent of atherosclerosis observed. This obstacle emphasizes again the importance of the electrocardiographic evidence in population studies of CHD.

In 1934 Levy et al. [57] observed that in the interval from 1920 to 1930 the autopsy experience of the pathology department of the Presbyterian Hospital in New York showed little increase of coronary artery disease although the clinical records indicated an increase of 400 per cent in the diagnosis of CHD during this interval. The most acceptable evidence of the unique freedom of Oriental people from atherosclerosis was the tragic native war casualty material studied by Benjamin [58] and by Steiner [59] in Okinawa during World War II. The Okinawans were almost free of the disease, even the aged. The American battle casualties in Korea [60] revealed gross atherosclerosis in the coronary arteries of three-fourths of the men and these were mostly under age forty. In 1915 Mönckeberg [61] found essentially the same in young European soldiers. Yater et al. [62] have published extensive descriptions of the coronary artery disease in military men as collected by the Armed Forces Institute of Pathology. Schornagel [63] has reviewed the autopsy data collected in Rotterdam for the period from 1940 to 1951. There was a wartime decrease of myocardial infarction and especially a decrease of coronary thrombosis suggesting that the phenomenon may have been one involving thrombogenesis rather than atherogenesis. Morris [64] has discussed at length the question of whether the apparent increase of CHD since 1920 is related to a change of extent of atherosclerosis, or of thrombosis as a

complicating mechanism. Morris examined the autopsy material of London Hospital for the interval from 1908 to 1949. Using the reasonably objective criterion of aortic calcification he concluded that there was *less* atherosclerosis in the period from 1948 to 1949 than in the period from 1908 to 1912. He observes that if this conclusion is valid, in the face of increasing CHD, the emphasis in our studies should be not with atherogenesis but rather with thrombosis. If thrombosis is the problem then we may have a better explanation for the decrease of CHD death rate in subjects past sixty years of age when the accumulation of plaques has become maximal. It is not contended that atherosclerosis is unimportant but rather that some necessary critical level of atherosclerosis serves as the substratum for the mechanism of thrombosis. The crucial question is then "Has there been a lowering of the critical level of coronary atheroma?" That this is not the entire explanation of the mechanism of CHD is emphasized by the frequency with which typical sudden death occurs in men with coronary atheromas but without evidence of thrombosis or complete occlusion. These events, comprising perhaps a quarter of all deaths attributed to CHD, would seem best explained by the concept of a differential myocardial oxygenation which leads to fatal arrhythmia, as described by Beck and Leighninger [65].

CONCLUSIONS

All these considerations of the epidemiology of coronary heart disease lead to several personal impressions:

1. The available evidence indicates that the increase in coronary heart disease revealed by vital statistics is largely artificial.
2. The epidemiologic data suggest the need for laboratory investigation of the role of energy balance and physical activity in the development of coronary atherosclerosis and thrombosis.
3. New epidemiologic data are needed from prospective studies of populations which emphasize certain cultural differences. The literature abounds with uninterpretable retrospective studies, and especially autopsy series. There is a great need among medical scientists for a better appreciation of the advantages of the planned experiment. Epidemiologic data must meet three requirements to be useful: (1) the population studied must be described so that an independent worker could obtain a comparable group; (2) the methods must be reproducible; and (3) the data must be shown in sufficient detail so that independent analysts can evaluate them.
4. Epidemiology is apt not to be a decisive method for resolution of these problems of chronic disease despite the current popularity of this endeavor. At best, the method may supply a few clues and enough encouragement to gifted people who, by intuitive knowledge and industry, will find the answer in the laboratory. Those who propose that the models of epidemiologic method developed in the study of infectious disease may be directly applied to chronic disease do not perceive the unique obstacles presented by the slow time scale of coronary heart disease.

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Clinico-pathologic Conference

Cholecystectomy Followed by Ascites, Fever and Oliguria

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine, Preventive Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THIS housewife, fifty-one years of age, was admitted to Barnes Hospital for the first time on April 6, 1956 with the chief complaint of abdominal swelling of one month's duration. She died on April 9, 1956.

Her past history revealed that she had undergone a cholecystectomy at another hospital on February 19, 1956 because of abdominal symptoms of unknown character and moderate fatty food intolerance, both of five to six years' duration, thought to be secondary to previously demonstrated gallstones. Postoperatively she went into shock. The abdomen was re-opened. Blood was found in the peritoneal cavity. A ligature was placed around an arterial bleeder in the peritoneal cavity. The patient required eight blood transfusions of 500 ml. each. Recovery was slow. She ran a fever with temperature rises of 102° to 103°F. for some days; this was associated with abdominal discomfort, nausea and vomiting. She was discharged after two weeks. Anorexia and nausea, however, persisted. About March 15, 1956, she re-entered her home town hospital because of rapid swelling of the abdomen. Her temperature ranged between 101° to 102°F. She was somnolent. On March 30, 8,000 ml. of clear straw-colored fluid was removed by abdominal paracentesis. Following this procedure oliguria developed despite mercurial diuretics. The vomiting became worse. She was given 1,000 ml. of 5 per cent glucose in normal saline daily by parenteral route. Five days before admission to Barnes Hospital the blood non-protein nitrogen was 38 mg./100 ml., the total serum protein value was 5.9 gm./100 ml. and the albumin was 1.9 gm./100 ml. On the day before admission 1,600 ml. of fluid were removed from the stom-

ach by Wangenstein suction. The patient became increasingly drowsy. There was no jaundice. At no time were abdominal organs or masses palpated. There was no history of excessive alcoholic intake, previous jaundice, liver dysfunction, hematemesis, melena or abdominal pain other than as described; nor was there a history of recent exposure to infection or to hepatotoxins.

The patient's previous health had been good. She had undergone a uterine myomectomy and appendectomy thirteen years previously. She had had intermittent infections of the urinary tract for about twelve years.

On physical examination her temperature was 37°C.; pulse, 120; respirations, 20; blood pressure, 70 mm. Hg systolic. The diastolic pressure was not recorded. The patient was normally developed and well nourished. She appeared lethargic and acutely ill. The skin was dry over the trunk, but the extremities were cold and sweaty. There was no jaundice. No lymph node enlargement was present. The eyes were sunken, but were otherwise normal. The mucous membranes were dry. The chest was clear. The point of maximal impulse of the heart was 10 cm. to the left of the mid-sternal line in the 5th intercostal space; the rhythm was regular; the tones were faint and of poor quality; no murmurs were heard. The abdomen was markedly distended. Shifting dullness in the flanks and a fluid wave were demonstrable. No organs or masses could be palpated. No bowel sounds were heard. There was no peripheral edema. The nail beds were slightly cyanotic. The peripheral pulses were weak and thready. A severe vaginitis was present. The deep tendon reflexes were hypoactive. There was plantar flexion of the toes in response

to plantar stimulation. An asynchronous tremor with incoordination on finger to nose test was noted.

Laboratory data revealed the following: the hemoglobin was 14.2 gm./100 ml. The white blood cell count was 21,850 per cu. mm. with the following differential pattern: band forms, 3 per cent; polymorphonuclear leukocytes, 85 per cent; lymphocytes, 8 per cent; monocytes, 4 per cent. The urine pH was 5.0; there was 3 plus to 4 plus proteinuria and no glycosuria; 2 to 5 pus cells were seen per high power field in the centrifuged sediment. A cardiolipin reaction for syphilis was negative. The blood non-protein nitrogen was 49 mg./100 ml. and the serum electrolytes were as follows: sodium, 118; potassium, 7.0; carbon dioxide, 26.7; and chloride, 69 mEq./L. The electrocardiogram showed sinus tachycardia with periods of 1:1 response alternating with periods of 2:1 sino-auricular block. The prolonged atrio-ventricular and intraventricular conduction times and the high T waves were thought to be compatible with hyperkalemia.

On admission to the hospital the patient was placed on Wangenstein suction and achromycin.[®] The blood pressure did not respond to vasoxyl[®] or to norepinephrine. Because of the electrolyte abnormalities she was given 300 ml. of 5 per cent sodium chloride intravenously. After 100 ml. of this solution the electrocardiogram reverted to a more normal pattern. The tracing was now thought to be consistent with anterior myocardial infarction of uncertain duration. By midnight of the first hospital day she had received a total of 1,200 ml. of fluid containing 300 mEq. of both sodium and chloride and 500 ml. of blood. She had voided only 40 ml. of urine. By the next morning the serum electrolytes were as follows: sodium, 123; potassium, 5.1; chloride, 80; and carbon dioxide, 21.6 mEq./L. Calcium was 9.2 mg./100 ml. and phosphorus, 4.9 mg./100 ml. The non-protein nitrogen was 51 and cholesterol, 108 mg./100 ml.; total serum protein, 6.0 gm./100 ml.; albumin, 3.1; globulin, 2.9; alkaline phosphatase, 11.5 Bodansky units; cephalin cholesterol flocculation test, 2 plus, thymol turbidity, 3.1 units; total bilirubin, 1.3 mg./100 ml. with direct acting bilirubin, 0.4 mg./100 ml.; indirect acting bilirubin, 0.9 mg./100 ml. The serum glutamic-oxaloacetic transaminase was 31 units and the prothrombin time was 16 seconds with a control of 14 seconds. Urine collected by in-

dwelling catheter showed a specific gravity of 1.022; the pH was 5.0; there was a trace of protein and 2 plus glycosuria; 5 to 7 red cells and 3 to 4 pus cells per high power field were seen in the sediment following centrifugation. The blood pressure finally rose to near normal levels with the administration of nor-epinephrine and the urine output increased, totalling 570 ml. on the second hospital day. Fluid and electrolyte replacement were continued. A blotchy cyanosis of the left leg developed below the insertion of a femoral catheter. The temperature remained 37.6°C. and the pulse remained 90. On the morning of the third hospital day the non-protein nitrogen was 52 mg./100 ml. and the serum electrolytes were: sodium, 131.1; potassium, 4.6; carbon dioxide, 26.1; and chloride, 88 mEq./L. The hemoglobin was 12.5 gm./100 ml. and the white blood cell count was 29,800 per cu. mm. The pulse rose to 120. Basilar rales developed and the patient was started on digitalis. She seemed to be doing fairly well, but on the morning of the fourth hospital day she was found dead in bed, cyanotic, with hyperextension of the neck.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: This fifty-one year old woman was well until seven weeks prior to her death, except for five to six years of gall bladder symptoms. For these symptoms a cholecystectomy was performed. Immediately after the operation abdominal pain and shock developed necessitating surgical re-entry into the abdomen. Bleeding vessels were noted. A series of complicating events subsequently occurred which ultimately led to her death. It appears likely that the abrupt downhill course in this patient was directly related to the cholecystectomy and the ensuing complications. Consequently, I would like to start the discussion by considering the complications which may attend or follow cholecystectomy. First, however, I would like to have Dr. Charles review for us the anatomy of the region around the cystic and the common bile duct.

DR. C. M. CHARLES: The celiac axis gives off three branches. One of these is the hepatic artery which first provides the right gastric and then turns upward giving off the gastroduodenal. As the hepatic artery approaches the liver it divides into right and left branches. The cystic artery rises from the right hepatic branch. The distribution of the hepatic artery and of the

cystic artery varies greatly. In over 30 per cent of cases, an aberrant origin of the hepatic artery is found. The right hepatic artery may be displaced, originating from the superior mesenteric artery and may be ligated at its crossing of the cystic and common duct during cholecystectomy. Accessory hepatic arteries may also be found. Variations of the cystic artery are even more common than those of the hepatic arteries. In more than 20 per cent of persons it does not originate from the right hepatic artery, but from the left, the common hepatic or even the gastroduodenal artery or the celiac axis. In these instances it crosses the hepatic or common bile duct. Double cystic arteries occur in about one-fourth of persons. It is of import to note that in the triangle of Calot the cystic artery, the right hepatic artery, the cystic duct and the common bile duct are in close approximation.

DR. REINHARD: Dr. Lischer, would you comment on the probable cause of bleeding noted in this patient at the time of reoperation? Would you guess that hemorrhage was coming from the cystic artery or is it possible that the hepatic artery had inadvertently been traumatized?

DR. CARL LISCHER: The cystic artery can certainly bleed postoperatively. The ligature can come off or there may be an accessory cystic artery which was not ligated. Bleeding can also come from the liver bed. In addition the right hepatic artery is very easily mistaken for the cystic artery at times, especially when it is anterior to the common hepatic duct. I do not know how often the right hepatic artery is ligated but it most certainly does not lead to death in all cases. In the experimental animal, ligation of the hepatic artery can result in death. The use of antibiotics, however, has reduced the mortality in these animals. I found a case report in the *New Zealand and Australian Journal of Surgery* [1] in which the main hepatic artery as it lies in close approximation to the common duct was ligated because it had been eroded by a T-tube in the adjacent common duct. On reoperation of this patient six months later, the stump of the hepatic artery could be seen and biopsy of the liver revealed no evidence of gross or microscopic abnormality. It is important to note that if the hepatic artery is ligated close to its origin from the aorta there is less chance of liver damage ensuing. On the other hand, ligation

at the periphery produces greater probability of hepatic infarction.

DR. REINHARD: Infarction of the liver is rare, presumably because of the generous collateral circulation of the liver. In an article by Graham and Cannell [2] from the University of Toronto and published in the *British Journal of Surgery* a very interesting case is reported of accidental ligation of the hepatic artery. In addition a review of the world's literature totalling twenty-eight cases of hepatic artery ligation in man was described. Of the twenty-eight cases, six ligations occurred during cholecystectomy and were presumably accidental. In ten, ligation occurred during surgery for resection of the stomach for carcinoma or ulcer. In three it was a deliberate procedure because of rupture of the artery and in two because of aneurysm of the artery. In the remaining cases it was presumed to be for miscellaneous reasons, in most cases inadvertent. Of the twenty-eight patients, sixteen died and twelve recovered. It is significant that twelve of the sixteen patients who died following ligation did so within the first two weeks, so that in general one may say, if our patient had hepatic artery ligation and survived for three weeks her chances for recovery were good. In view of these reports it seems probable that our patient might well have been in the process of recovering from some operative hepatic vascular insult and that her death was due to another superimposed vascular event.

The clinical manifestations of ligation of the hepatic artery include pain in the hepatic region, tenderness over the liver with muscle spasticity, vomiting, fever and leukocytosis, jaundice and hemorrhagic manifestations associated with hypoprothrombinemia. Hepatic infarction when it does occur may lead to subsequent abscess formation. In our patient, pain was present but it was not localized over the hepatic region. There was no muscle tenderness or spasticity and jaundice was only minimal. In addition, there was no hypoprothrombinemia. There was fever and striking leukocytosis. Dr. Shank, were the liver function tests, the ascites and the other manifestations here compatible with hepatic infarction?

DR. ROBERT SHANK: Although the changes in liver function were only of a moderate degree I do not think that infarction of the liver can be eliminated. It seems to me that ascites accom-

¹ WYNDHAM, N. R. Gross damage to the portal vein and hepatic artery during cholecystectomy. *Australian & New Zealand J. of Surg.*, 25: 292, 1956.

² GRAHAM, R. R. and CANNELL, D. Accidental ligation of the hepatic artery. *Brit. J. Surg.*, 20: 566, 1933.

panying ligation of the hepatic artery could occur only if there were co-existing factors present such as hepatic disease, cirrhosis or some other complicating feature.

DR. REINHARD: One would have to attribute the ascites then to some other complication and not to simple hepatic infarction secondary to hepatic artery ligation. Dr. Shank, you saw the patient in the hospital and wrote a note stating that you thought portal vein thrombosis was a possibility.

DR. SHANK: When we saw this patient we took the approach that you have taken today. That is, that the events which developed were related to the surgery. We thought it was most likely that there was involvement of the portal vein rather than of the hepatic artery. Obstruction of the portal vein can be secondary to thrombosis and be associated with infection as well. Fever and leukocytosis may occur in uninfected portal system thrombi as well as in infected ones. On the other hand, the fever persisted for a long time in this patient so we suspected the possibility of hepatic abscesses following infected portal vein thrombosis. Ascites as a consequence of long standing portal vein thrombosis is certainly not a rarity.

DR. REINHARD: This patient did not have an enlarged spleen or hematemesis.

DR. SHANK: Yes, that is disturbing and there were also no signs of venous anastomoses upon the abdominal wall.

DR. REINHARD: In Dr. Popper's recent book [3] I came across the statement that contrary to previously held opinions, occlusion of the portal vein at surgery does not produce serious consequences. He suggests that symptoms of shock, ascites and death previously ascribed to this lesion are really due to thromboses extending into the mesenteric and splenic veins; such extension of the thrombotic process is, of course, a common accompaniment of portal vein thrombosis.

Dr. Butcher, what do you think was the primary lesion in this patient?

DR. HARVEY BUTCHER: From the evidence presented, I am rather opposed to ligation of the hepatic artery, or injury, as a major diagnosis and after listening to Dr. Shank I doubt that this patient had portal vein thrombosis. The protocol can be explained, if one postulates injury to the bile ducts with a bile leak and a sub-hepatic,

subphrenic, or lesser sac collection of bile with a localized bile peritonitis. Abscess formation and ascites in this situation can be explained by the fact that associated with such collections of bile in the abdomen, we occasionally see the outpouring of peritoneal fluid in that portion of the peritoneal cavity which is not directly involved by the process.

DR. REINHARD: You are not disturbed then by the accumulation of 8 L. of clear fluid?

DR. BUTCHER: No. This fluid might have been removed from the free peritoneal cavity and not from the localized bile collection. Very little is stated about the abdominal findings. Is there any additional information?

DR. REINHARD: Apparently there was so much abdominal fluid that examination of the abdomen was not entirely satisfactory.

DR. SHANK: This patient was moribund when we saw her. She did seem to have diffuse hepatic tenderness but there was no real localization. Neither the liver nor the spleen could be palpated.

DR. REINHARD: Dr. Butcher, would you comment on the therapy? I get the impression that perhaps fluid replacement was suboptimal.

DR. BUTCHER: It appears that the deficit in extracellular fluid was quite severe. As I understand it the patient received only 1,200 ml. of isotonic fluid plus 300 ml. of 5 per cent NaCl solution on the day of admission. This quantity would seem to be insufficient replacement.

DR. REINHARD: The patient was also severely hypotensive and unresponsive to nor-epinephrine. Dr. Perry, does this suggest also that the patient was suffering from hypovolemia?

DR. MITCHELL PERRY: The combination of hyponatremia and hypovolemia certainly may explain the hypotension and its failure to respond to nor-epinephrine.

DR. REINHARD: Dr. Price, would you discuss this patient's electrocardiograms?

DR. KENNETH PRICE: The changes are compatible with an acute anterior myocardial infarction. There was sinus rhythm with inter-ventricular conduction delay and a supraventricular tachycardia. However, the effect of electrolyte imbalance cannot be completely evaluated in these electrocardiographic changes.

DR. REINHARD: It appears possible, then, that the patient either had a coronary thrombosis or coronary arteriosclerosis with shock and subsequent myocardial infarction.

Dr. Recant, would you discuss the oliguria?

³ POPPER, H. and SCHAFFNER, F. *Liver: Structure and Function*. New York, 1957. McGraw-Hill.

DR. LILLIAN RECENT: Apparently oliguria developed immediately following the removal of a large volume of ascitic fluid. Ascites influences renal function, producing in some cases diminished glomerular filtration, diminished renal blood flow and sodium retention. The presumption is that the very rapidly accumulating ascites induced striking changes in renal hemodynamics in this patient. In addition to the effect of the ascites *per se* the abrupt removal of large volumes of ascitic fluid with subsequent reaccumulation, resulted in hyponatremia and hypovolemia. The latter probably produced a further diminution in the volume of flow through the kidney. I suspect that despite the past history indicative of renal infection, that in all probability no serious pre-existing renal disease was present. The final development of azotemia was probably related to the period of shock, hyponatremia and hypovolemia.

DR. REINHARD: Dr. Bricker, would you comment on the electrolyte and volume changes?

DR. NEAL BRICKER: The initial event in the evolution of these changes was probably the formation of ascites. In response to the decrease in effective extracellular fluid volume, it may be postulated that a volume control system was activated resulting in the renal retention of salt and water, presumably to meet the needs of the organism. With the removal of 8 L. of ascitic fluid and the subsequent reaccumulation, one would assume that the volume control system was activated, resulting in antidiuretic hormone release (despite decreasing tonicity) which promoted maximal water retention. Presumably at this time, also, the amount of water permitted, was out of proportion to that of sodium. Hence, she continued to expand total extracellular fluid volume hypotonically and a progressive hyponatremia developed. Finally, after the large amount of ascites was removed, fluid rapidly reaccumulated in the intraperitoneal space, and resulted in intravascular hypovolemia, hypotension and eventually peripheral vascular collapse and oliguria.

DR. REINHARD: The anatomic changes produced in the kidney were what?

DR. BRICKER: Certainly sustained hypotension may result in acute tubular necrosis. However, in view of the fact that the urinary output was recorded at over 500 ml. on the day following hypotension I would expect to find no large scale tubular disease. Probably there will be flat based healed scars suggestive of old pyelo-

nephritis but I would think that the kidneys would show no major lesion which contributed to her death.

DR. REINHARD: After several days in the hospital, the patient seemed to be improving when something happened which caused her very sudden death. Dr. Butcher, would you comment?

DR. BUTCHER: With a femoral catheter in place for two to three days followed by the development of a cyanotic swollen leg on the same side one might expect a local thrombophlebitis and perhaps a massive pulmonary embolus terminally. May I ask Dr. Moore if the electrocardiographic findings influenced the volume of fluid replacement?

DR. CARL V. MOORE: The implication has been made several times that this woman might have received a smaller volume of fluid than was indicated. It must be emphasized, however, that she had electrocardiographic evidence suggestive of acute myocardial infarction. Though she was not in obvious congestive failure, it was certainly a real possibility that overloading the circulation could induce pulmonary edema. It is a mistake to leave the impression that it would have been highly desirable to give this woman another 2 or 3 L. of fluid parenterally under these circumstances. Dr. Bricker, would you comment?

DR. BRICKER: I agree with your comments and would like to add one other point. At the time of admission this patient was oliguric and there was no assurance that her urine volume would increase with elevation of her blood pressure to a level sufficient to affect filtration. Thus, overzealous fluid administration on the day of admission might well have been hazardous, if the oliguria persisted.

DR. REINHARD: In summary, the course of events in this patient appeared to be the following: she was relatively well except for gall bladder complaints. She had a cholecystectomy following which there was intra-abdominal hemorrhage which I would guess was probably associated with cystic artery bleeding. The patient went into shock. The abdomen was reopened and the ruptured artery was tied off. Following the second surgical procedure ascites and profound electrolyte and fluid imbalance developed. I am inclined to believe that infection in the vicinity of the common bile duct, the portal vein and adjacent structures played an important part in the lesion. Portal vein occlu-

sion probably occurred. If there were infarcts within the liver, they may well have become converted into abscesses. Myocardial infarction probably occurred sometime during the terminal illness. The terminal event seems to be best explained by a pulmonary embolus and the discussion of the renal lesion, I believe, needs no further comment except that it was probably secondary to the electrolyte changes, fluid depletion and shock.

PATHOLOGIC DISCUSSION

DR. WALTER BAUER: At the time of autopsy it was noted that no evidence of icterus could be seen on external examination. The paracentesis incisions were all on the right side of the abdomen. The abdominal cavity was found to be partitioned into two compartments of roughly equal size by a bile-stained membrane which extended from the undersurface of the liver down over contiguous loops of small bowel into the pelvis on the left side and then up over the parietal structures on the left lateral wall of the abdomen to the diaphragm. The abdominal surface of the diaphragm on the left formed the superior surface of the compartment. The membrane measuring up to 0.5 cm. in thickness was in continuity with the gallbladder bed, the porta hepatis and extended through the foramen of Winslow into the lesser sac.

Within this membrane-lined compartment, 3,000 cc. of greenish serofibrinous fluid was found. The right side of the abdomen was entirely dry.

Close inspection of the biliary tree showed a completely normal common and left hepatic bile duct. The right hepatic bile duct was transected and its distal end ligated along with a short stump of the cystic duct. The proximal end of the right hepatic duct was open to the abdominal cavity. All branches of the hepatic artery were identified and only the cystic artery was found ligated. No thrombosis of the portal vein or infarcts of the liver were seen. In summary of the abdominal findings, bile drained into the abdomen by way of the transected right hepatic bile duct, down along the porta hepatis through the foramen of Winslow into the lesser sac and from there, or by direct extension along the porta hepatis, to the root of the mesentery to the left side of the abdomen.

No thrombi were found in the coronary arteries and no gross evidence of a myocardial infarct.

A mural thrombus was found in the region of the femoral vein catheter and one small recent thrombus was found in a small branch of the right pulmonary artery without an associated infarct. The lungs were only slightly congested and contained a small amount of thin fluid. The kidneys were of normal size without scars and had a distinct pallor to the cortex. There were only minor changes in the remainder of the visceral organs and no lesions were found in the brain.

DR. NADYA KONIKOV: One of the most interesting findings, in view of the electrocardiogram, was a normal myocardium without evidence of infarction or interstitial infiltrate. The iliac vein contained a recent thrombus, and there was a moderate inflammation of the underlying vein wall, suggesting that it was traumatized by the catheter. A recent pulmonary embolus of microscopic size was lying in a small pulmonary artery.

The wall of the transected right hepatic duct showed no inflammation. Where bile spilled from the transected end there was bile staining of the peritoneal surface and a mild associated inflammatory reaction. The membrane (Fig. 1) which assisted in the loculation of bile was stained accordingly and fibrous but exhibited only minimal inflammatory reaction, consistent with a sterile bile peritonitis. Small round cells and some large histiocytes were present; most of them contained bile pigment. The serosal surface of a portion of colon which did not lie in the bile-stained cavity showed an organized fibrous peritonitis, with some slight bile staining and occasional pigment laden macrophages.

The lobular pattern of the liver was well preserved. Portal areas contained a mild degree of round cell infiltration, such as one might see with any intraperitoneal infection. A few large washed-out nuclei of hepatic cells indicated the presence of glycogen. About the gallbladder bed there was bile staining and a few very small accumulations of hemosiderin pigment, but no indications of recent hemorrhage.

There was slight evidence in the kidney of tubular damage at least ten days old. In a few convoluted tubules there were dark proteinaceous casts, sloughing of epithelial cells, numbers of epithelial giant cells and occasionally calcification of the epithelium. (Fig. 2.) Recent damage was evidenced by presence of some proteinaceous casts in the distal convoluted tubules, a moderate amount of interstitial edema, and round cell infiltrate, chiefly at the corti-

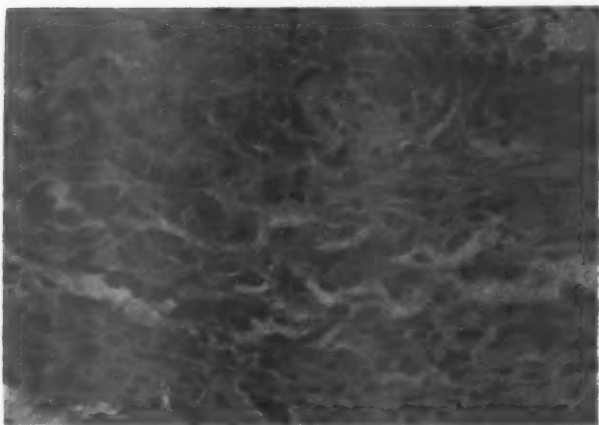


FIG. 1. Bile-stained membrane, note the minimal cellular inflammatory reaction with only a few small round cells and large histiocytes containing bile pigment. Hematoxylin and eosin stain.

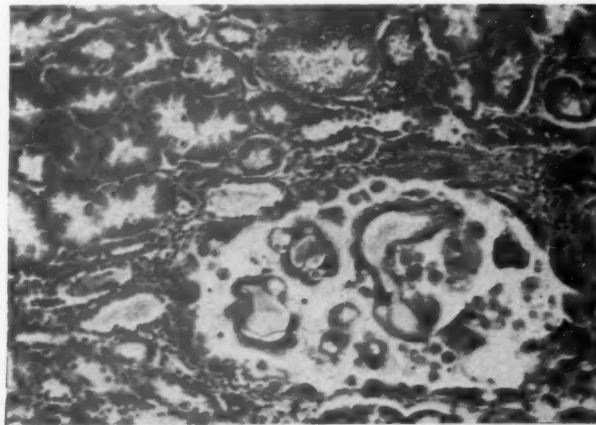


FIG. 2. Convoluted renal tubules showing proteinaceous casts, sloughing of cells, epithelial giant cells and calcification of the epithelium. Hematoxylin and eosin stain.

comedullary junction, all suggesting hypoxic nephrosis. There was also a scattered recent degenerative lesion of the proximal convoluted tubules, perhaps not more than twenty-four hours old, with marked vacuolization of the tubular epithelium and focal loss of nuclei. (Fig. 3.)

Comparison of the fat content of the adrenal (oil red O Stain) of this patient with that of a patient of the same age and sex who died acutely, confirms the impression of moderate lipoid depletion.

In summary, the right hepatic duct was ligated at cholecystectomy. The symptoms developing shortly before death were caused by bile peritonitis. By the sixth week of the course the bile had become loculated, and clear fluid was obtained by tapping the major cavity. Renal tubular damage was slight, and estimated to vary from twenty-four hours to ten days in duration.

Final anatomic diagnoses: Primary: transection of the right hepatic duct; bile peritonitis with loculation, membrane formation and 3,000 ml. of green serofibrinous exudate confined to the left half of the abdomen; 23 cm. right hypochondrial paramedian healed surgical incision; two right lumbar paracentesis scars; congestion and edema of lung, 850 gm.; hypoxic nephrosis, remote, with tubular degeneration, and recent with hydropic tubular

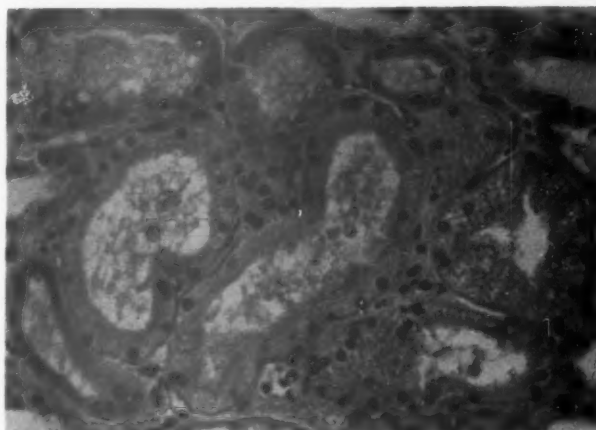


FIG. 3. Recent renal tubular damage with marked vacuolization of the tubular epithelium and focal loss of nuclei. Hematoxylin and eosin stain.

degeneration; needle puncture wound of right groin (history of indwelling femoral catheter); recent thrombus formation in right iliac vein; edema of right leg; minute recent thrombus in small pulmonary artery; acute ulcers in the hypopharynx and lower esophagus (history of intubation); petechiae and ecchymoses of the mucosa of the stomach, small and large intestine and urinary bladder; lipoid depletion of adrenal, moderate. Accessory: arteriosclerosis of aorta, coronary and splenic arteries, slight; sclerosis of anterior leaflet of mitral valve, slight; colloid adenomas of right lobe of thyroid.

Case Reports

An Illustrative Case of Chronic Pyelonephritis with Persistently Hypotonic Urine*

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THE importance of chronic pyelonephritis as a cause of Bright's disease was generally unrecognized as late as 1930. Such authorities on the kidney as Volhard and Fahr omitted it from their classification of "Die Brightsche Nierenkrankheit" [7]. It was not until the classic clinico-pathologic studies in the 1930's by Longcope [2,3] and Weiss and Parker [4] that the significance of this insidious lesion and its cardiovascular consequences were emphasized. The experimental studies of Mallory, Crane and Edwards [5] confirmed the basic histology of pyelonephritis and the importance of obstruction of the urinary tract in its pathogenesis. More recently, these fundamental contributions have stimulated a re-evaluation of the bacteriology and treatment [5,7], pathogenesis [8] and clinical characteristics [9] of this extremely common chronic renal disorder.

The following case offered an opportunity to observe some important characteristics of the natural history of this disease, to apply certain principles of specific antibiotic therapy and to evaluate an unusual instance of disturbed tubular function.

CASE REPORT

E. M., a forty-two year old white machinist, was admitted to the Medical Service of the New Haven Hospital for the first time in November, 1954. He had visited a urologist in 1942 following an insurance examination in the course of which pus cells were found in his urine. At that time he complained of a dull, aching pain in the left flank of six months' duration. He had no other symptoms and no other significant genitourinary history. Cystoscopy disclosed slight redness of the mucous membrane of the bladder. The bladder urine showed a specific gravity of 1.016, a

trace of albumin, a few pus cells, a few bacilli and an occasional red blood cell. Microscopic examination of the urine from the right kidney was negative; that from the left kidney showed moderate numbers of pus cells and bacilli and an occasional red blood cell. Cultures from the left and right kidney showed no growth; however, bladder urine grew out non-hemolytic streptococci (enterococci). The left kidney excreted 25 per cent of phenolsulfonphthalein in fifteen minutes; the right kidney 15 per cent in fifteen minutes. Appearance time was five minutes on each side. Retrograde pyelograms revealed no abnormalities.

The patient was told to take 1 gm. of sulfadiazine three times a day for five days and to return in six months. He did not return and was completely asymptomatic during the next ten years.

In December, 1952, following an auto accident, he was hospitalized for one day. Urinalysis showed a specific gravity of 1.010, 2+ albumin, 1 to 4 white blood cells, an occasional red blood cell, and few bacteria. Hemoglobin was 12.5 gm. per cent. He had no symptoms referable to his genitourinary system.

Subsequent to this accident, the patient never regained full health. He noted progressive weakness, lethargy, moderate anorexia, polydipsia, polyuria and nocturia and weight loss. In June, 1954, he was hospitalized in a nearby city because of anemia of undetermined etiology and occult blood in his stool. The patient was subjected to an exploratory laparotomy for questionable intra-abdominal malignancy. No abnormalities were found. From June, 1954, until his admission to the New Haven Hospital in November, 1954, the patient required thirty-three blood transfusions. He also noted dizziness, tremor, staggering gait and headaches in addition to progression of his other symptoms. For a two-week period prior to admission, nausea and vomiting had occurred two to three times daily.

Physical examination revealed a well developed, moderately well nourished man who appeared pale

* From Yale University School of Medicine, Department of Internal Medicine, New Haven, Connecticut. Aided by grants from the U. S. Public Health Service and the American Heart Association and a contract (MD-116) with the Office of the Surgeon-General, Department of the Army.

† Established Investigator of the American Heart Association.

TABLE I
TESTS OF URINARY DILUTION AND CONCENTRATION IN A PATIENT WITH CHRONIC PYELONEPHRITIS WITH
PERSISTENTLY HYPOTONIC URINE

Time (min.)	Urine Volume (cc./min.)	Urine Osmol- arity (mOsm/L.)	Serum* Osmol- arity (mOsm/L.)	C _{creatinine} (cc./min.)	C _{urea} (cc./min.)	C _{inulin} (cc./min.)	Filtered† Water Excreted (%)	Filtered† Osmolarity Excreted (%)
<i>Study I</i>								
0 1,000 cc. (H ₂ O orally)
60	3.8	220	304	5.3	5.3	5.2	73	53
120	3.4	217	298	4.5	4.8	5.0	68	49
180‡	3.5	227	298	4.6	5.3	4.8	73	51
240‡	2.7	226	303	6.1	...	5.2	52	39
<i>Study II</i>								
60	2.7	208	293	3.9	4.1
120	2.0	204	289
180§	3.5	215	289	5.0	5.2
240§	3.5	233	290	5.0	5.2
360	3.2	224	292	4.3	4.7

* Determined by freezing point depression using a Fiske osmometer.

† Assuming that the inulin clearance (C_{inulin}) equals glomerular filtration rate.

‡ 250 milliunits pitressin® infused intravenously per hour.

§ 150 cc. 3 per cent NaCl + 250 milliunits pitressin infused intravenously per hour.

and chronically ill. The blood pressure was 140/80 and never rose higher than 148/88. Fundi showed moderate A-V nicking. The skin had poor turgor, was dry and slightly scaling. The heart and lungs had no abnormalities. The spleen tip was felt 1 to 2 cm. below the costal margin on deep inspiration. The kidneys were not palpable and there was no tenderness in the costovertebral angle. There was a coarse tremor of the outstretched hands with intermittent twitching of various muscle groups. No other neurologic abnormalities were noted.

Urinalysis during the initial hospitalization and on all subsequent examinations generally disclosed the following pattern: acid reaction, specific gravity 1.004 to 1.008, albumin 1+ to 3+, sediments 0-rare red blood cell, 0 to 6 white blood cells, rare hyaline casts per high power field. On many occasions the sediment was completely normal. Excretion of phenolsulphthalein dye was less than 20 per cent in two hours. The red blood count was 2.56 million, hemoglobin 7.2 gm., hematocrit 21 per cent. Bleeding time, clotting time and clot retraction were normal. Coombs' test was negative; osmotic fragility of red cells and urinary urobilinogen were normal. A red blood cell survival study using Cr⁵¹ disclosed a markedly accelerated rate of destruction (half time = fifteen days; normal = twenty-eight to thirty-one days).

Blood non-protein nitrogen was 218 mg. per cent,

serum sodium 125 mEq./L., serum potassium 4.8 mEq./L., serum chloride 101.5 mEq./L., serum bicarbonate 10.0 mEq./L., serum calcium 8.0 mg. per cent, serum inorganic phosphorus 13.2 mg. per cent, serum total proteins 6.86 gm. per cent with albumin 4.15 and globulin 2.71 gm. per cent.

Initial urinary cultures showed a moderate to heavy growth of enterococci. This organism was moderately sensitive to chloromycetin,[®] extremely sensitive to erythromycin, but resistant to all other antibiotics.

After correction of anemia by transfusions of packed erythrocytes and treatment of his acidosis by parenteral administration of sodium bicarbonate, the patient showed remarkable symptomatic improvement. However, polyuria and polydipsia continued, with urine volumes of 2 to 3 L. daily. He was discharged after ten days, on sodium bicarbonate, 8 gm., 25 per cent solution of calcium chloride, 25 cc., and a high carbohydrate diet with 50 gm. of protein, per day.

Over a period of one month his non-protein nitrogen fell from 218 to 119 mg. per cent. At the end of this time, in spite of a ten day course of 0.5 gm. of chloromycetin per day combined with 2 gm. of erythromycin per day, enterococci were still present in the urine. Quantitative bacterial cultures disclosed 50,000 organisms per cc. of urine which were still sensitive to chloromycetin and erythromycin and



FIG. 1. Representative section from the kidney showing interstitial fibrosis, cellular reaction, dilated tubules with eosinophilic colloid casts, and periglomerular fibrosis, typical of chronic pyelonephritis.

resistant to penicillin and streptomycin. In spite of these *in vitro* indications of sensitivity it was decided to treat the patient in the hospital with 1,200,000 units of procaine penicillin and 1 gm. of streptomycin daily for a ten-day period. Cultures of the urine were negative for the first time after this therapy, as were all subsequent cultures during the next three months prior to his death.

Studies to evaluate his polyuria and relatively low urinary specific gravity were undertaken in December, 1954, when it was thought that his renal function had temporarily stabilized at its maximum level. Tests of renal function during this admission are summarized in Table 1.

Subsequent to this hospitalization and during the next three months the patient's course slowly but progressively deteriorated. He required 3 to 4 units of packed erythrocytes per month to maintain a hemoglobin concentration of 11 to 12 gm. per cent. His spleen remained palpable.

Congestive heart failure developed with slowly progressive dyspnea, orthopnea and edema of the legs. This responded poorly to digitalization and restriction of his intake of sodium bicarbonate. He was readmitted for the last time six months after his initial hospitalization because of progressive uremia (non-protein nitrogen 190 mg. per cent), uncontrollable nausea, vomiting, muscular twitching, stupor and congestive failure, all of which responded poorly to therapy. He died ten days after admission.

At postmortem there was moderate edema of the

lower extremities and the periorbital area. In each pleural space there were 500 cc. of clear yellow fluid. When the pericardium was incised a rough granular yellow exudate on both surfaces was seen; there were fine pericardial adhesions and approximately 50 cc. of cloudy yellow fluid. The heart was enlarged (600 gm.). The ventricular cavities appeared dilated. The right ventricular wall measured 3 mm. and the left 14 mm. in thickness. The coronary arteries showed significant atherosclerosis with considerable calcification. There were no valvular deformities. Microscopic examination disclosed hypertrophy of muscle fibers with mild focal fibrosis. The epicardial surface was covered with a fibrinous exudate infiltrated with lymphocytes and mononuclear cells. Both lungs were non-crepitant, congested and doughy; the right weighed 625 gm. and the left 650 gm. Microscopic examination revealed a heavy accumulation of hemosiderin-laden macrophages in the air spaces. There was congestion and early fibrosis of the alveolar walls. The spleen was enlarged and weighed 425 gm. Its capsule was smooth and shiny and the cut surface was dark red in color with prominent Malpighian follicles. Microscopically, reticular hyperplasia was seen throughout, with large littoral cells lining the sinusoids heavily infiltrated with hemosiderin.

The right kidney weighed 125 gm. and the left 110 gm. The left kidney was pale and firm. The capsule stripped with some difficulty revealing a coarsely granular surface and a moderate number of small cysts (2 to 5 mm. in diameter) filled with clear fluid.

The cut surface showed a pale, hard, narrowed cortex 3 mm. in thickness and a pale medulla. The pelvis was not dilated but the mucosa was thickened, dull and edematous. The right kidney was similar to the left with the exception that the only cyst was at the lower pole, measuring 20 mm. in diameter, filled with clear fluid. Microscopic examination showed extensive interstitial scarring of both kidneys (Fig. 1) with marked diminution in the number of glomeruli and tubules. There was widespread periglomerular fibrosis and the glomeruli showed varying degrees of partial to complete hyalinization. The interstitial tissue was infiltrated with lymphocytes, particularly in the subcapsular area. The remaining tubules were atrophic, dilated, and in many cases filled with eosinophilic luminal casts or precipitates ("colloid casts"). The arteries showed varying degrees of arterio- and arteriolo-sclerosis. There was thickening, fibrosis and lymphocytic infiltration of calyceal submucosa. The cysts were lined by a fibrous capsule and a single layer of cuboidal epithelium.

The final anatomic diagnosis was bilaterally contracted and scarred kidneys, secondary to chronic pyelonephritis; cardiomegaly; pulmonary congestion and edema; hemosiderosis of spleen, lungs and liver.

COMMENTS

This case represents a striking example of the manner in which chronic infection may lead to progressive destruction of the renal parenchyma with few or no symptoms referable to the genitourinary tract [3,9]. The only symptom manifested prior to 1952 was an ache in the left flank ten years before the patient's death, at which time he had normal renal function, although an enterococcal infection of the genitourinary tract had apparently become established. It is not clear why, in the kidneys, organisms like the enterococcus as well as *B. coli* and *M. pyogenes* should at times produce slowly progressive destruction, characterized clinically by chronicity and the absence of local symptoms and pathologically by diffuse scarring and fibrosis, rather than the acute pyogenic manifestations which characterize their invasion of other parts of the body [8].

It is easy to understand how in the absence of localizing symptoms the diagnosis could have been confused with that of an intra-abdominal malignancy or a primary hematologic disorder, such as malignant lymphoma or primary refractory anemia with splenomegaly. The correct diagnosis was initially obscured not only by the severity of anemia characterized by rapid destruction of red blood cells but by the innocent appearance of the urinary sediment, which may be normal or almost normal in chronic pyelo-

nephritis, especially when concentrating power has been impaired and the urine is dilute. Splenomegaly has been reported to occur frequently in pyelonephritis [4,10]. The enlarged spleen in the present case was caused by reticulo-endothelial hyperplasia and marked hemosiderosis and was associated with recurrent anemia and rapid destruction of erythrocytes. Birchall and Alexander [9] have stressed the finding of anemia out of proportion to the degree of uremia as an important characteristic of chronic renal infection. It would be of interest to determine whether or not splenic enlargement in this disease could be correlated with the more severe grades of anemia.

The bacteriologic data in the present case suggest that urinary infection with enterococcus had existed at least since 1942. When cultured and tested for antibiotic sensitivity in 1954, this organism was found to be very sensitive *in vitro* to erythromycin and chloromycetin but resistant to penicillin and to streptomycin. Despite these findings the organism was not eradicated by an intensive course of the former drugs, but readily succumbed to a combination of penicillin and streptomycin. These results emphasize the value of bactericidal combinations in treating indolent infection, as well as the danger inherent in predicting therapeutic response from *in vitro* tests of sensitivity and the need for testing combinations of antibiotic in sensitivity studies.

Prominent symptoms during the last two years of the patient's illness were persistent polyuria (3 to 4 L./day) and polydipsia. Although progressive encroachment on renal reserve commonly results in fixation of urinary specific gravity, urinary solute concentration under these circumstances generally remains equal to or slightly higher than the solute concentration of an ultrafiltrate of serum. Repeated determinations of urinary specific gravity in the present case disclosed values consistently between 1.004 and 1.008, concentrations which would be expected during mild water diuresis in normal subjects. Persistent hyposthenuria was confirmed by the studies summarized in Table 1, which indicated the following: (1) clearances of inulin, urea and creatinine approximated 5 cc./min., indicating a reduction in functioning renal mass to about $\frac{1}{20}$ of its original size; (2) this contracted population of nephrons consistently elaborated a urine considerably more dilute than the serum; (3) there was no appreciable further dilution of the urine or increase in urinary flow subsequent to the oral ingestion of 1000 cc. of

water and no concentration of the urine after infusion of pitressin; and (4) the administration of hypertonic saline caused a moderate increase in urinary flow and concentration, a response qualitatively similar to that which would occur in a subject with diabetes insipidus who was given an osmotic load.

It is clear that this patient's kidneys, although elaborating hypotonic urine, were unable to respond to exogenous or endogenous anti-diuretic hormone. This state has been called "water-losing nephritis" [77]. Because of the severe reduction in glomerular filtration, losses of water through the kidneys in this patient did not reach the magnitude observed in untreated diabetes insipidus or in nephrogenic diabetes insipidus of the congenital variety [72].

The pathogenesis of this kind of "nephrogenic diabetes insipidus" is probably twofold. In the first place, even in the few functioning nephrons which remain, renal cells of the distal and collecting tubules at the site where urine is normally concentrated are probably distorted and rendered partially or completely functionless by the underlying inflammatory process. Indeed, Oliver has pointed out that dissected nephrons from patients with chronic nephritis bear little resemblance to those from normal kidneys [73]. Secondly, because the glomerular area available for filtration is so greatly reduced, each filtering unit must excrete water and solutes in such great volume as possibly to preclude complete equilibration of hypotonic urine in the loop of Henle and to force its delivery in the dilute rather than the isotonic state to the site of final concentration. Anslow and Wesson [74] have demonstrated that the normal dog, even while under the influence of pitressin, may transiently excrete a hypotonic urine during intense osmotic diuresis. As can be deduced from Table 1, if a normal subject with a glomerular filtration rate of 120 cc./min. excreted water and solute in proportion to his inulin clearance at the same rate as did this patient, he would pass 80 cc. of urine containing 18 mO_s. per minute. Such rates are almost impossible to attain experimentally in normal man and it is therefore not clear whether or not under such unusual circumstances normal human kidneys might excrete a urine hypotonic to serum.

The systematic study of many cases of chronic renal disease with technics which directly measure the osmolarity of the urine and serum might disclose that this type of functional defect is more common than hitherto considered and may

enable its pathogenesis to be more precisely determined.

SUMMARY

The natural history of an illustrative case of chronic pyelonephritis is presented. The following features are of interest: (1) a completely asymptomatic period of ten years during which the renal parenchyma was almost completely destroyed by infection with the enterococcus; (2) failure of the infection to respond to erythromycin and chloromycetin in spite of *in vitro* sensitivity to these antibiotics and its subsequent eradication with penicillin and streptomycin to which it had displayed resistance *in vitro*; (3) splenomegaly and hemolytic anemia for which no explanation other than chronic pyelonephritis could be found; and (4) the presence of polyuria with a persistently hypotonic urine of fixed concentration which did not respond to exogenous or endogenous anti-diuretic hormone.

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Adenocarcinoma Occurring in Regional Jeunitis*

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SINCE the initial description of regional enteritis about twenty-five years ago [1], an extensive literature has appeared on all phases of the subject. However, we believe this communication and a previous one by one of us [2] are the only reported instances of carcinoma occurring at the site of segmental stenosing, granulomatous jeunitis. In view of the rare incidence of jejunal carcinoma in general, one may speculate whether or not carcinoma of the jejunum represents a hitherto unrecognized complication of jeunitis.

CASE REPORTS

CASE 1. A thirty-six year old white woman was admitted to The Mount Sinai Hospital in February, 1955. She was suffering from upper abdominal pain, persistent vomiting, loss of weight and marked weakness. Her initial gastrointestinal symptoms, characterized mainly by severe diarrhea, were first manifested eight years previously. At that time she was admitted to another institution where radiologic studies revealed evidence of colitis. A laparotomy, performed at the same hospital, revealed an inflamed large intestine and surgery was limited to an appendectomy. Post-operatively she was treated with a low residue diet, antibiotics, multivitamin preparations and paregoric. Nevertheless she continued to have four or five watery bowel movements daily which, however, never showed evidence of blood, pus or unusual quantities of mucus. Her nutritional status continued to deteriorate; over a period of two years her weight fell from 125 to 75 pounds. At this time (1949) she consulted one of us (D. A.) and was treated with aureomycin® and small doses of cortisone; her condition improved. The diarrhea ceased and she regained 40 pounds in a few months. In 1953, x-ray studies revealed a "combined" form of segmental enterocolitis. A number of involved loops were present in the proximal jejunum. (Fig. 1.) The terminal ileum showed the typical radiologic findings associated with regional ileitis. A barium enema showed inflammatory involvement of the left transverse and the proximal descending colon. (Fig. 2.) In spite of the radiologic evidence of widespread disease, the patient remained well enough (on steroid

therapy) to be fully employed as an active business secretary for a period of almost five years.

In February, 1955, eight years after the onset of her intestinal symptoms, an exacerbation marked by persistent vomiting, abdominal cramps and weight loss necessitated her first admission to The Mount



FIG. 1. Case 1. Small bowel series four years prior to death. Note areas of marked narrowing indicating multiple segments of stenosing jeunitis. (Courtesy Dr. S. WEISKOPF.)

Sinai Hospital. The physical examination was within normal limits except for obvious malnutrition and moderate dehydration. Radiologic studies of the gastrointestinal tract at this time revealed considerable gastric distention and dilatation of the entire duodenum proximal to the ligament of Treitz. (Fig.

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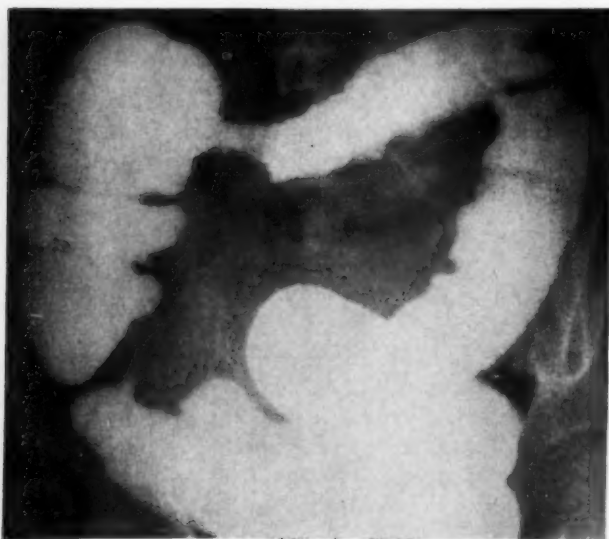


FIG. 2. Case 1. Narrowed segment in the mid-transverse colon with limited distensibility and irregularity of contour; coarse mucosal pattern of the distal transverse colon and splenic flexure. Marked narrowing of terminal ileum; terminal ileitis. (Courtesy Dr. S. WEISKOPF.)



FIG. 3. Case 1. Marked gastric and duodenal dilatation. There is an irregular, markedly stenotic segment of jejunum just beyond the ligament of Treitz (upper arrow on left of patient). In addition there are areas of marked narrowing with intervening dilatation in the jejunum. A Levine tube is seen in the stomach.



FIG. 4. Case 1. Multiple areas of irregularity and narrowing of jejunum.

3.) Marked progression had taken place in the pathologic condition of the upper jejunum. Just distal to the ligament of Treitz, marked narrowing of the jejunum was noted which extended distally in a tortuous fashion for a distance of about 10 cm. A small localized collar-button collection of barium was found in the

distal portion of this segment. This area of involvement was followed by a dilated loop of jejunum characterized by a slight irregularity of the mucosa and retained secretions. Immediately beyond this point another short segment of constant narrowing was noted. (Fig. 4.) No further abnormalities were noted in the small bowel but in the terminal ileum narrowing, rigidity and mucosal destruction were again encountered. In the colon, loss of haustral pattern, mucosal destruction and narrowing were found to involve the distal two-thirds of the transverse colon and the proximal descending colon. Comparison with previous films indicated that the ileal and colonic lesions had remained practically static. Attention was therefore directed to treatment of the newly developed jejunal obstruction. Institution of gastric suction, administration of intravenous fluids, blood transfusions and a high caloric, low residue diet were followed by marked clinical improvement. This led to the belief that the symptoms were due to a perhaps temporary exacerbation of the jejunal inflammatory process. Since operative therapy did not appear to be promising in such a widely disseminated ileocolitis, continuation of medical therapy was decided upon.

Following temporary improvement for four months readmission became necessary in June, 1955, because of recurrence of persistent vomiting in even more aggravated form than previously. Dehydration and chemical evidence of a hypochloremic alkalosis were present on admission along with the clinical picture of mild shock. These conditions were rapidly corrected by appropriate intravenous therapy and the patient underwent laparotomy (L. G.).

The clinical picture at this time was attributed



FIG. 5. Case I. Napkin ring-like tumor encircling the jejunum, just distal to the ligament of Treitz.

to obstruction resulting from progression of the inflammatory lesion in the jejunum and a duodeno-jejunosomy was contemplated for the relief of a benign stenosis. At operation, preliminary exploration of the colon and terminal ileum revealed the pre-operative radiologic findings to be due to chronic localized inflammatory involvement. Neither of these lesions appeared to be contributing materially to the clinical picture. Attention was then turned to the proximal jejunum. Three distinct zones of involvement were noted. Beginning immediately distal to the fossa of Treitz, the jejunum for a distance of a few inches was stony-hard and narrowed. The induration extended into the beginning of the small intestinal mesentery. Distal to this point there was a segment of dilated and somewhat thickened small intestine. This was followed by another narrowed, thickened, short loop of bowel which, however, felt quite different from the stony hardness noted in the upper involved segment. The entire duodenum was greatly dilated and considerably thickened, obviously a result of the obstruction commencing near the duodenojejunal angle. The stony hardness of the upper obstructed area led to the suspicion that a carcinoma had developed at that point and the feasibility of resection was investigated. It soon became evident that a radical resection was impossible because of extension of disease to the roots of the mesentery and upward over the pancreas in the vicinity of the main superior mesenteric trunks. A retrocolic anastomosis was then performed between the transverse portion of the duodenum to the right of the superior mesenteric vessels and the bowel immediately beyond the involved jejunum. Because of previous experience (Case II) with a jejunal carcinoma complicating regional jejunitis, the liver was carefully explored but

no evidence of metastases was noted. Following operation the patient made an uneventful recovery and was discharged on the eleventh postoperative day with practically complete disappearance of symptoms.

Although the patient continued to be free of gastrointestinal symptoms, anorexia and malnutrition developed and she was readmitted five months after her last operation. Examination at this time revealed a large, hard, irregular liver which, clinically, was obviously carcinomatous. A percutaneous liver biopsy with a Vim-Silverman needle revealed metastatic adenocarcinoma. The patient's condition deteriorated rapidly, ascites developed and she died a month later. She showed no symptoms of intestinal obstruction during this terminal period.

Post mortem examination revealed a granular cobblestone appearance of the jejunal mucosa just distal to the ligament of Treitz, with thickening of the submucosa and the muscularis. In the center of this region an ulcerated, polypoid, flat based, encircling carcinoma, measuring 5 cm., was found which extended directly into the mesentery. (Fig. 5.) Microscopic views showed adenocarcinoma cells arising within an area of jejunitis. (Fig. 6.) There were also numerous metastases involving the peripancreatic and periaortic lymph nodes, both lungs and pleurae, and several vertebral bodies. The liver weighed 6,000 gm. and was extensively replaced by tumor tissue. The surgical anastomosis was widely patent.

CASE II. This case was previously reported in detail by one of us [2]. The patient was a thirty year old white man who was admitted to the Beth Israel Hospital with a clinical picture of acute obstruction of the upper small intestine. Over a period of nineteen years (since the age of eleven), he had been afflicted



FIG. 6. Case 1. Low power view showing adenocarcinoma arising immediately adjacent to an area of jejunitis and invading all layers of bowel wall. Original magnification, $\times 6$.

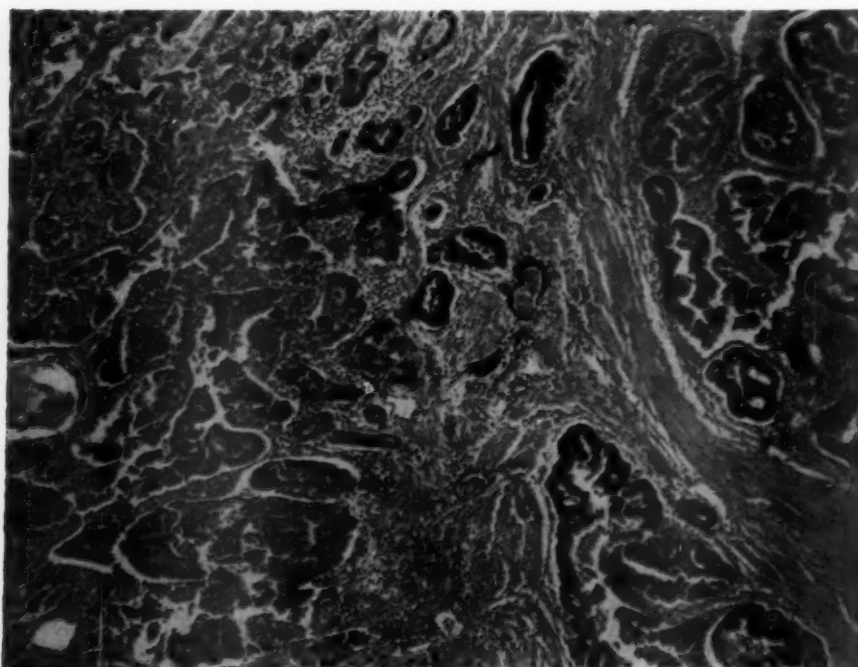


FIG. 7. Case 1. Magnification view revealing adenocarcinoma in the mucosa and invading the bowel wall. Original magnification, $\times 325$.

with recurrent episodes of abdominal cramps, non-bloody diarrhea and weight loss. At the age of eighteen he was told that he had ulcerative colitis (on what basis is not clear) and was treated with sedation and a low residue diet, with good results. However, following his induction into the army at the age of nineteen his symptoms recurred. Thorough studies at this time revealed no objective evidences of disease and the patient was discharged with the diagnosis of psychoneurosis.

At the age of twenty-six, following a period of relative improvement, an appendectomy was performed elsewhere, for reasons not apparent. Following this procedure diarrhea, anorexia and periods of constipation recurred. Finally, after almost nineteen years

of illness and several months prior to this admission for acute intestinal obstruction, x-ray studies revealed an inflammatory disease limited to the upper jejunum.

Upon admission, roentgenograms revealed a number of jejunal loops tremendously distended with gas in which wide fluid levels were present. Concomitantly, there was complete absence of gas in the colon. A long intestinal tube was passed and reached the jejunum just distal to the fossa of Treitz. Following decompression of the bowel and reestablishment of normal fluid and salt balance the patient was operated upon. A series of stenosing lesions were found in the proximal jejunum, with extreme dilatation of the bowel between them. The most proximal lesion was located approximately 18 inches distal to the ligament

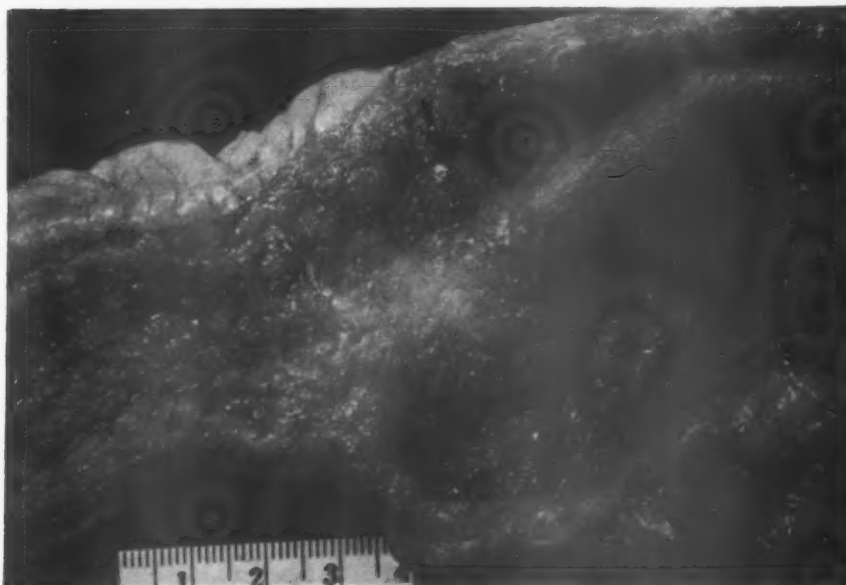


FIG. 8. Case II. Arrow points to adenocarcinoma. (From GINZBURG, L., SCHNEIDER, K. M., DREIZIN, D. H. and LEVINSON, C. Carcinoma of the jejunum occurring in a case of regional enteritis. *Surgery*, 39: 347, 1956.)

of Treitz and the most distal one about 6 feet away. The bowel from a point approximately a foot distal to the ligament of Treitz to a point just distal to the last stenotic lesion was resected and a lateral anastomosis performed.

The pathologic examination revealed that the zones of constriction were due to the presence of typical regional enteritis. (Fig. 7.) However, at the junction of one of the constricted zones with a dilated segment, an unusually firm indurated nodule, about 2 cm. in diameter, was discovered which had not been noted at operation. (Fig. 8.) Histologic examination revealed that this lesion was a papillary adenocarcinoma. No evidence of metastasis was observed in any of the glands resected with the specimen.

The patient did well for approximately six months and had a remission of his gastrointestinal symptoms. Shortly thereafter he was readmitted because of fever and epigastric pain. Physical examination revealed a rather tender mass in the left epigastrium. At laparotomy a number of large metastatic masses were found in the left lobe of the liver as well as smaller metastatic nodules in the right lobe. Tissue removed by biopsy proved to be metastatic carcinoma of the liver resembling that of the jejunal carcinoma. The patient died a few months later with generalized carcinomatosis.

SUMMARY OF CASES

1. Two cases of carcinoma of the jejunum originating in segments of bowel affected by regional jejunitis are reported. Both were characterized by the development of early and widespread postoperative metastases.

2. The first case occurred in a patient suffer-

ing from a combined form of enterocolitis in which the proximal jejunum, terminal ileum and left transverse and descending colon had been the site of more or less static segmental granulomatous lesions for approximately seven years. Exacerbation of symptoms was misinterpreted as due to progression of the inflammatory process in the proximal jejunum. Exploration finally revealed that the obstructive symptoms were the result of a malignancy which had advanced to the state of inoperability.

3. Case II had a history of eighteen years' duration before objective evidence of disease limited to the upper jejunum became obvious. At operation following an episode of acute intestinal obstruction, multiple stenotic segments with marked intervening dilation were present in the upper jejunum and limited to that portion of the bowel. A small carcinoma, about 2 cm. in diameter, was an unexpected pathologic finding and probably not responsible for the clinical symptoms. In spite of the wide resection of this small lesion, extensive hepatic metastases were noted six months postoperatively.

COMMENTS

Carcinoma of the small bowel is a rare disease. According to Ewing about 3 per cent of all gastrointestinal malignancies occur in the small intestine and of these adenocarcinoma is the most common type. If one omits the ampullary and

periampullary lesions in the duodenum, then the jejunum becomes the most common site. Cameron [3], reviewing 105 carcinomas of the jejunum and ileum, found 40 per cent of the lesions to be in the first quarter of the jejunum and 28 per cent in the distal quarter of the ileum. Yet Raiford [4], reviewing 56,500 autopsies and surgical specimens, found only sixteen cases of carcinoma of the small bowel (duodenum included) and four of these were in the jejunum. The overall incidence of small bowel malignancies varies between 0.03 and 0.5 per cent of autopsies performed. At The Mount Sinai Hospital only nine primary adenocarcinomas of the jejunum are on record during the past thirty years (one of these occurring in the case of regional jejunitis herein reported), while at the Beth Israel Hospital one of four operated cases of jejunal carcinoma was associated with regional jejunitis in the last ten years. The occurrence of two of thirteen cases of carcinoma of the jejunum in patients with regional jejunitis brings up the question of a causal relationship between these two conditions.

While there are no recorded cases of carcinoma occurring in regional ileitis, a far more common form of the disease, Hughes [5] has reported a case of terminal ileitis in which a reticulum cell sarcoma developed. However, the appearance of inflammatory polyps in areas of small bowel where the mucosa was incompletely denuded by the basic disease process has been reported [6]. The possibility of malignant changes occurring in adenomatous polyps of the small bowel has been known for over thirty years [7] although such carcinomatous transformation has never been reported in small bowel inflammatory pseudopolyps. It is of interest that most of the reported large series of small bowel malignancies antedate the period during which the concept of regional enteritis became current. Therefore the role of regional jejunitis in such cases cannot be assayed. However, in a number of instances cellular infiltrates and mucosal atrophy surrounding the malignant lesions have been discovered. There is, of course, no way of determining whether these changes were due to an antecedent inflammatory lesion or whether they occurred subsequent to the carcinoma.

It should be further noted that the carcinomas in both our cases arose in the proximal jejunum and had the character of a flat-based polypoid lesion. Although pseudopolypoid changes are less frequent in regional enteritis than in ulcerative colitis, it is conceivable that the jejunum *per se*, when involved by granulomatous inflammation, may represent a more susceptible area for carcinomatous transformation of inflammatory polyps than has hitherto been recognized.

The significance of the development of obstruction in a known case of regional jejunitis deserves comment. While Case II and three other operated cases of regional jejunitis were typically inflammatory and cicatrizing in character, one may infer from Case I that a malignancy should always be suspected in this area and should lead to a careful exploration.

Finally, our two cases seem to bear out the experience of other observers who have commented on the rapid downhill course of jejunal carcinoma. Both our patients died within a few months after a carcinoma was discovered at operation.

SUMMARY

Two cases of regional jejunitis are reported in which a primary adenocarcinoma developed at the site of a stenosing jejunitis in the proximal jejunum. It is suggested that adenocarcinoma may be a complication of granulomatous jejunitis.

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Aplastic Anemia Fourteen Years Following Administration of Thorotrast*

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WITH the advent and ready accessibility of radioactive compounds for use in medical, military and industrial enterprises, there has been an associated interest in the long term effect of such materials. While thorium is now a potential breeder material in the production of atomic energy, it has been used for over twenty-five years in the form of a colloidal suspension called thorotrast.[®] Thorium has a half-life of 1.4×10^{10} years and it breaks down into the subproducts of mesothorium, thorium X, and thorium A, B and C. According to Reeves and Stuck, thorium emits alpha, beta and gamma radiation; approximately 95 per cent of the total energy is emitted as alpha radiation, this radiation being sharply localized [7]. They state that the alpha particles of mesothorium and the products of its decay have a greater velocity and penetration power than those of radium.

Prezyna, Ayres and Mulry state that the total radioactivity of thorotrast decreases over a period of eight years; however, it then begins to rise, due to the fact that sufficient radiothorium has broken down to form other members of this radioactive family, which are strong alpha emitters [2]. They report that the resultant total radioactivity after ten years is 54 per cent of the activity of the original sol, and that this activity rises from this level to reach a peak activity in another fifteen years.

The usual amount of thorotrast used for hepatosplenography, 75 cc., has an estimated alpha ray equivalent of 1.4 μ g. of radium [3]. Studies of radium poisoning have indicated that 0.5 to 2 μ g. of radium have proved fatal [3].

Looney and Colodzin state that shortly after thorotrast is given to a patient it is concentrated in the reticuloendothelial system, notably in the liver, spleen and bone marrow, practically all the thorotrast remaining there throughout the life of the patient [4]. In these organs larger and

larger aggregates of thorotrast develop. The short range of the dangerous alpha particle in relation to the size of the thorotrast aggregate may explain, in part, the relative lack of destruction found in autopsy material. This is especially true in the liver. However, in the spleen progressive destruction takes place, with loss of splenic architecture and replacement with fibrosis and, finally, a reduction in splenic size. Minor skeletal changes have been reported by Looney and Colodzin in over 50 per cent of seventeen patients who received thorotrast, but a definite relationship has not been established.

The uses of thorotrast have covered a wide range. It has been utilized in cerebral arteriography, peripheral angiography, hepatosplenography, myelography, encephalography, ventriculography, retrograde pyelography, mammography, gastrointestinal roentgenography, salpingography, cholangiography, bronchography, placentography, and visualization of sinuses and sinus tracts [5]. Nevertheless, the use of thorotrast has been controversial since its inception. Most of the uses of thorotrast cited have been abandoned. Recently, its use in locating accessory spleens in selected hematologic disorders has been recommended, but in emergency situations only [6]. Its major use today is in cerebral angiography, for which it has been described by some as the agent of choice, but by others regarded as too dangerous [5].

Over the past quarter of a century there have been frequent reports and investigations concerning the possibility of late, harmful effects following the use of thorotrast. Yater and Coe in 1943, after ten years' experience with over 300 cases, stated that they could find no immediate or remote ill effects of importance [7]. After completing a survey in 1951, covering 4,325 cases, Thomas, Henry and Kaplan could report only the occurrence of late fibrosis in the liver and

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spleen, and scar formation at the sites of perivascular extravasation of the thorotrast injection [8]. Cassel, Ruffin, Reeves and Stoddard reported no important deleterious late effects in three patients studied seventeen, sixteen and thirteen years, respectively, after thorotrast administration [9].

However, there have been other reports testifying to serious late effects of thorotrast. Rube and Mehl reported a patient who required nephrectomy twenty-three years after a retrograde pyelogram with thorotrast had been taken [10]. Histologic changes demonstrated that the renal changes necessitating nephrectomy were due to thorotrast. In a survey of the literature Looney and Colodzin state that five deaths from primary hepatic tumors have been reported following its use; they add one case of their own, and mention two others that have been brought to their attention [4]. These authors also state that malignant tumors developed in five patients at the sites of injection of thorotrast; in two patients after injection into the lacrimal ducts, in one after injection into the maxillary sinus, in one after a retrograde pyelogram, and in one after injection into the ducts of the breast. They state further that there have been four cases of leukemia and eight of aplastic anemia following its use. Spier [11], Laborde [12] and Hieronymi [13] have each reported cases of aplastic anemia.

The following case presentation is of a patient with aplastic anemia starting fourteen years subsequent to the use of thorotrast.

CASE REPORT

A fifty-four year old white man was admitted to the hospital on April 26, 1956, with the chief complaint of chest pain of three to four weeks' duration. In the six weeks prior to admission the patient noted several episodes of epistaxis. In this same period he had severe headaches, shortness of breath and syncope on several occasions. Finally, precordial chest pain developed, typical of angina of effort. The angina, as it became more severe and frequent, necessitated admitting the patient to the hospital.

The past history revealed that he had had a thyroidectomy in 1933 for a "goiter." In 1942 the patient was given thorotrast, administered intravenously for visualization of the liver and spleen. Shortly thereafter, cholecystectomy was performed. In 1946 he had a ureteral stone removed at cystoscopy. The patient was admitted to this hospital in 1953 for evaluation of his hypertension, and was soon discharged after a brief investigation. In the same year symptoms of right cerebral thrombosis developed, but these were of brief duration. Nothing in the patient's history indi-

cated that he ever had been exposed to any hematopoietic toxin other than thorotrast. He was known to be a consistent drinker of alcoholic beverages. The family history was non-contributory.

Physical examination revealed a temperature of 98.2°F., pulse 88 per minute, respiratory rate 18 per minute and blood pressure 170/95. The patient appeared sallow and chronically ill. There was a nodule, hard and fixed, about 2 cm. in diameter in the right antecubital fossa. The fundoscopic examination showed A-V nicking. The neck had a scar from a previous thyroidectomy. The lungs and heart revealed no abnormal physical signs. The abdominal examination revealed a right rectus incisional scar and a liver edge that was 2 to 3 cm. below the right costal margin. The rest of the examination was normal.

The laboratory data were as follows: Hematologic findings on October, 16, 1953, were hemoglobin 14.0 gm. per 100 cc., white blood cells 6,000 per cu. mm., with a normal differential count. On April 17, 1956, the hemoglobin was 12 gm. per 100 cc., with 2,820,000 red blood cells per cu. mm., packed cell volume of 28 per cent, 5,700 white blood cells per cu. mm., with 20 per cent neutrophils, 78 per cent lymphocytes and 2 per cent monocytes. On April 24, the hemoglobin was 7.5 gm. per 100 cc., with 2,290,000 red blood cells per cu. mm., packed cell volume of 24 per cent, and a platelet count of 53,000 per cu. mm. On April 27, the hemoglobin was 6.0 gm. per 100 cc., with 1,820,000 red blood cells per cu. mm., a packed cell volume of 21 per cent and a white blood cell count of 4,800 per cu. mm. with 30 per cent neutrophils, 3 per cent stab forms, 65 per cent lymphocytes and 2 per cent monocytes, and a platelet count of 100,000. On April 30, the packed cell volume dropped to 18 per cent, the lowest recorded.

The urinalysis was normal, as were the bleeding, clotting, and prothrombin times, the reticulocyte count, clot retraction, cell fragility, direct Coombs' test, L. E. cell test preparations, serum protein, albumin and globulin, icterus index, cephalin flocculation and alkaline phosphatase. There was no evidence of blood in the urine, feces or gastric juices. The bromsulphalein showed 7.4 per cent and 10 per cent dye retention at forty-five minutes on the two occasions it was tested. The significance of this amount of retention of bromsulphalein is uncertain, in view of the fact that the patient was a consistent drinker of alcoholic beverages. However, Looney reports that in three cases there was an alteration of the bromsulphalein retention test in his series of thirty-five patients who had received thorotrast [4].

Three sternal and iliac crest bone marrow aspirations were attempted during the first two days of hospitalization; they revealed fat globules and very few marrow cells.

An x-ray of the abdomen revealed a marked increase in density of both the liver and the spleen, the latter shadow being very small. Adjacent to the liver

and spleen were some scattered densities, probably representing thorotrast in lymph nodes which drained these organs. An x-ray of the right antecubital fossa revealed a 2 by 3½ cm. collection of radiopaque material representing perivascular extravasation of thorotrast. The patient was scanned to determine whether gamma rays were present, and these were found to be located over the upper abdomen and the right elbow.

During the patient's hospital course of four and one-half months the white blood count varied between 2,000 and 6,600 per cu. mm., averaging 3,300 during the first forty days, and 4,460 during the last two months; the granulocytes averaged 840 during the first forty days, and 1,550 during the last two months. During the first three weeks the patient required 13 units of blood, averaging 2 units of blood every three days. During the next 110 days the patient received 11 units of blood, averaging 1 unit every ten days. According to Stickney and Hanlon, at normal rates of red cell destruction a transfusion of 500 cc. of whole blood every seven to ten days should maintain the level of hemoglobin if the recipient's bone marrow is totally inactive [14]. This patient's blood requirements have ranged within this measure of maintenance.

Some thought was given to the idea that it might be possible to remove the thorotrast by a chelating agent. Foremen has used the calcium di-sodium salt of ethylenediaminetetracetic acid (EDTA) to remove plutonium in two cases of plutonium poisoning [15,16]. The first patient who was treated had recent exposure to plutonium but the second patient was exposed seven years prior to the institution of therapy; nevertheless, satisfactory results were obtained in both cases.

After the patient had been in the hospital for three weeks, 4 gm. of EDTA were given in 5 per cent glucose solution, daily, for five consecutive days. This was repeated two months later in the same amount. A twenty-four-hour control sample of urine and a twenty-four-hour sample while the patient was receiving EDTA were tested. There was no difference in radioactivity when the urines were checked with a Geiger counter. This result implies that the patient did not benefit from this therapy. However, since the date of the first infusion of EDTA a marked drop in the need of whole blood transfusions has occurred; there also has been a simultaneous increase in the number of granulocytes, as well as an increase in the total number of leukocytes. These differences are often seen during the course of aplastic anemia and, since there was no detectable urinary output of a radioactive substance, it is doubtful that the changes were the result of the use of EDTA.

SUMMARY

The status of the use and long term effect of thorotrast is reviewed.

A case is presented of a patient with aplastic anemia following the use of thorotrast fourteen years before. An attempt to correct the aplastic anemia by using EDTA to remove the thorotrast appears to have been ineffective.

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"Periodic Fever"*

Occurrence in Five Generations

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OUR interest in the so-called "periodic diseases" was first stimulated by the recognition and study in this clinic of patients with regularly recurring febrile episodes secondary to cyclic neutropenia [7]. It was with this phenomenon as the possible underlying mechanism that the five generation family to be reported here was referred to us for evaluation and diagnosis in 1953.

"Periodic fever" has been reported as an independent clinical entity in the medical literature [2-32]. Some cases have been considered to have a psychogenic origin [2], in others allergy has been implicated [3], in still others mild chronic infections have been found [4]. Periodic fever has been described in pulmonary tuberculosis [5], in periarteritis nodosa [6] and in association with malignant reticulosis [7-11].

Reimann [12-18] has thoroughly reviewed this problem and presented his own observations on periodic fever as a form of periodic disease, noting an hereditary incidence in many of his cases. Other reports also refer to the familial incidence of this syndrome [19-27].

CASE REPORTS

CASE 1. D. T., a fifty-two year old white male school teacher, was first seen in our clinic on June 10, 1953. The patient complained of recurrent attacks of fever, noted since birth. These febrile episodes had occurred regularly at approximately twenty-one- to twenty-eight-day intervals, lasting from three to five days. The patient stated that during the early stages of the attacks his head felt "heavy and congested" and he experienced a feeling of pressure throughout his body. This was followed by chills and fever with the temperature often reaching 103°F. or higher. General malaise, constipation, and a stiffness and soreness of all joints were common. During the peak of the attack he noticed circular as well as irregularly outlined areas of redness of the skin over the entire trunk. As a rule the patient was unable to

perform his regular duties as a school teacher and had to remain at home in bed. After three to five days all symptoms subsided and the patient returned to a normal state of health. The recurrence of these attacks was unrelated to any detectable external influence or subjective emotional factors or associated with any food idiosyncrasies. The patient had never lost consciousness or had convulsions, delirium, visual disturbances or ataxia during the attacks.

On physical examination between attacks the patient, a slightly obese male, did not appear ill. His temperature was 98.5°F. and blood pressure was 110/60 mm. Hg. Examination of the eyes, ears, nose and mouth revealed no abnormalities and the lungs were clear. No organs or masses were palpable on abdominal examination. Examination of the genitalia showed the left testicle to be in the inguinal canal and it could not be brought out through the external ring.

During the febrile episodes the patient appeared acutely ill. There was some injection of the conjunctivas. The skin of the entire trunk showed the presence of irregular and circular erythematous lesions. The temperature was 103°F. The blood pressure was 110/60 mm. Hg. The rest of the physical examination was within normal limits.

Blood counts taken during as well as between attacks were essentially the same and were within the normal range. The total red blood cell count was 4.73 million per cu. mm.; hemoglobin, 12.9 gm. per cent; total white blood cells, 9,700 with 79 per cent polymorphonuclear cells; 3 per cent eosinophils; 16 per cent lymphocytes and 2 per cent monocytes; reticulocytes, 0.4 per cent; platelets, 506,000 per cu. mm. and the hematocrit was 44 per cent. The corrected sedimentation rate was 1.0 mm. per minute (normal: 0.1 to 0.3 mm. per minute). The direct Coombs' test and blood Kahn reaction were negative. The serum calcium was 9.6 mg. per cent; inorganic phosphorus, 3.2 mg. per cent; total bilirubin, 0.3 mg. per cent; sodium, 147 mEq./L.; serum potassium, 4.9 mEq./L.; chloride, 102 mEq./L. The fasting blood sugar was 86 mg. per cent; total protein, 6.3 per cent; albumin, 3.6 per cent and globulin, 2.7 per cent. Examination of the stools was negative for ova and parasites. Repeated blood, urine and stool cultures,

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and cultures of secretions obtained from the throat during the febrile episodes, were negative. Agglutinations for typhoid H and O, paratyphoid A and B and brucella were all negative. The antistreptolysin titer was not increased. Chest x-rays and x-rays of the skull were both normal.

Electrophoretic studies of the serum showed an increase of alpha-2-globulin to 1.6 times the normal level and an increased gamma globulin of 2.0 times normal. These changes were persistent during and between the episodes of fever. The serum lipoproteins were normal.

Electroencephalograms obtained during and between attacks were the same and they were interpreted as abnormal because of shifting of the temporal slow wave activity.

CASE II. L. T., a seventeen year old white male, son of D. T. (Case I), was first seen at our clinic as an outpatient on June 10, 1953. His chief complaint was periodic episodes of fever lasting from three to five days every twenty-one to twenty-eight days. Fever was accompanied by malaise, constipation, soreness of muscles and joints, and irregular areas of redness over the skin on the trunk. During the febrile episodes the patient felt ill and many times was unable to attend school. Between bouts of fever he had no complaints. His parents had noticed that the patient had had these episodes since birth. These attacks had not apparently been influenced by any external or emotional factors nor were they related to any kind of food intake.

The past history was not remarkable. The patient had had a tonsillectomy performed as a prophylactic measure. Examination of the patient during an attack revealed an acutely ill person with some injection of the conjunctivas. The temperature was 102.8°F., pulse 110 per minute and blood pressure 110/70 mm. Hg. Irregular and circular erythematous lesions were present over the entire trunk. The lungs, heart, mouth and throat were normal. Neither the spleen or other masses were palpable in the abdomen. No lymph nodes were felt. The neurologic examination was normal.

Physical examination between the attacks revealed a normal young male.

Blood counts taken during and after the attacks were essentially the same and in the normal range. The total red blood cells were 4.82 million per cu. mm.; hemoglobin, 13.7 gm. per cent; reticulocytes, 1.8 per cent; platelets, 539,840 per cu. mm.; total white blood cells, 7,850 with 73 per cent polymorphonuclear cells, 1 per cent eosinophils; 21 per cent lymphocytes and 5 per cent monocytes. The hematocrit was 46 per cent. The corrected sedimentation rate was 0.5 mm. per min. A direct Coombs' test was negative. The serum inorganic phosphorus was 3.5 mg. per cent; total bilirubin, 0.5 mg. per cent; total protein, 6.7 per cent; albumin, 4.5 per cent and globulin, 2.2 per cent. The stool was negative for ova and para-

sites. Repeated cultures from urine, blood and stool, and from secretions obtained from the throat during the febrile episodes, were negative. Typhoid, paratyphoid and brucella agglutinations were negative. The antistreptolysin titer was not increased. Chest x-ray and x-ray of skull were both normal.

Electrophoretic analysis showed an increase in alpha-2-globulin and gamma globulin both during and after the episodes of fever. The serum lipoproteins were normal.

Electroencephalograms taken during and between the episodes of fever were the same, showing a number of minor wave formations and other irregularities of pattern in the temporal regions. In October, 1954, this patient received a minor skull injury in a fall; this was followed by three episodes of "blackout" of short duration without convulsions.

CASE III. G. T., an eighty-two year old white man, is the father of D. T. (Case I) and grandfather of L. T. (Case II). The patient was first seen in our clinic in October, 1955. He had had attacks of fever similar to the ones described by his son and grandson. Febrile episodes had been present as long as he could remember. This elderly and alert man was found to be normal on physical examination between attacks. During the febrile episodes he appeared acutely ill with some injection of the conjunctivas, erythematous lesions of the skin, and temperature of 103.2°F. All laboratory tests on this patient, such as blood counts, phosphorus, phosphatase, total protein, albumin, globulin, bilirubin, calcium, phosphorus and hematocrit were normal. Cultures from blood, urine, stool, and from secretions obtained from the throat during the febrile episodes, were negative. Agglutinations for typhoid, paratyphoid and brucella were also reported as negative. Electrophoresis showed an increase in alpha-2 and gamma globulins. The serum lipoproteins were normal. One electroencephalogram was interpreted as normal.

FAMILY HISTORY

Figure 1 is a schematic representation of the familial incidence of periodic fever in five generations of this family.

From the history obtained from G. T. (Case III) it is evident that his father and grandfather had this same periodic fever all their lives. His mother was normal. His five sisters all have had periodic episodes of fever with characteristics similar to those in Case III. Three sisters had remained single and of these three, two are dead and one is alive. The other two sisters are married to normal persons. One of the married sisters has only one son, and he is normal. The other married sister has one son and one daughter; both are free of symptoms of periodic fever. The normal daughter has four normal children.

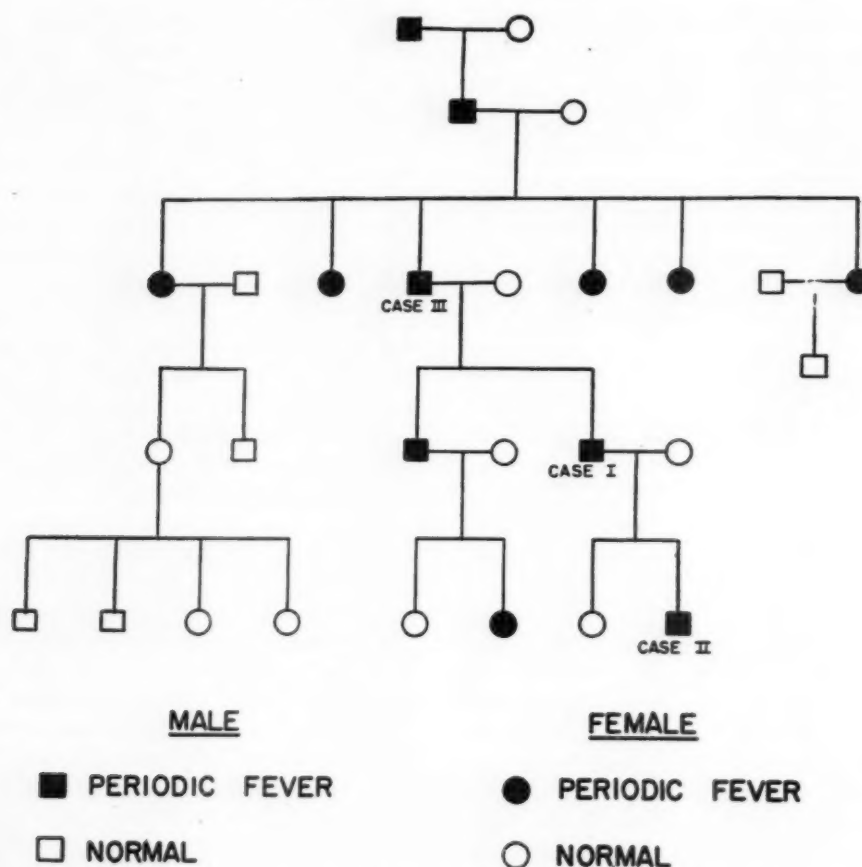


FIG. 1. Schematic representation of the incidence of periodic fever in five generations of the same family.

G. T. (Case III) married a normal woman. They had two sons: one is D. T. (Case I), who is married to a normal woman, and has one son (Case II) with periodic fever, and one normal daughter. The other son of G. T. (Case III) also has episodes of periodic fever; he is married to a normal woman and has two daughters, one with periodic fever and one free of symptoms.

It is inferred that periodic fever is an inherited trait in this family. The mode of transmission is consistent with the idea that the trait is dependent upon a dominant, autosomal gene. This family is of German-Dutch ancestry.

THERAPY

In view of the findings on the electroencephalograms of D. T. and L. T. (Cases I and II), these patients were given dilantin® and phenobarbital. No improvement of their symptoms of periodic fever was obtained with this therapy.

Cortisone, ACTH and/or prednisone were given to all three patients and there was marked improvement of symptoms. In the beginning, treatment consisted of 100 mg. of cortisone daily

for ten consecutive days. Later the patients were given cortisone or prednisone only during the days of the attack of fever.

D. T. (Case I) has been receiving corticosteroid therapy during the episodes of periodic fever for the past three years. He is at present taking prednisone. The doses of prednisone required to control his symptoms are 20 mg. the first day, 10 to 15 mg. the second day and 5 to 10 mg. the third day of his fever. On this therapeutic regimen the symptoms of periodic fever were relieved and this patient has been able, for the first time in his life, to work full time in his job as a school teacher. No side effects have been observed from this medication.

After ten days of corticosteroid therapy for each of three consecutive attacks, L. T. (Case II) experienced no further febrile episodes, with the exception of sporadic, mild attacks which responded promptly to 10 to 15 mg. of prednisone administered on the first day of fever.

Patient G. T. (Case III) has also obtained marked improvement of symptoms on prednisone therapy during the one year of observation.

EXPERIMENTAL STUDIES

We have attempted to clarify the possible mechanisms influencing the production of these episodes of fever. In order to investigate the possibility of a hormone or toxin circulating in the peripheral blood of the patient during the febrile episodes the following experiment was carried out in Case II. A total of 500 cc. of whole blood was obtained from the patient by venesection during one of his febrile episodes, when the temperature had reached 103°F. The blood was stored at the blood bank and after seven days was transfused back into the same patient. No febrile reaction or any of the symptoms of periodic fever developed in this patient during or after the autoblood transfusion.

Funduscopy examination of this same patient was done during and after the febrile episode in order to rule out the possibility of vascular spasm. However, no abnormalities of the vessels of the retina were observed at any time.

COMMENTS

The cause of periodic fever is unknown. In the patients considered in this communication such factors as allergy [3], psychogenic factors [2] and chronic infections [4] have been carefully ruled out. Tuberculosis [5], periarteritis nodosa [6] and malignant reticulosis [7-11] also were ruled out by clinical, laboratory and x-ray studies.

The hereditary incidence of periodic fever in the members of this family favors the possibility of a congenital defect affecting the thermoregulatory center of the brain. However, it is difficult to explain with this hypothesis the periodicity of the attacks. An alternative possibility is the influence of some endocrine disturbance inducing these periodic changes. It is possible that this influence might be manifested as vasomotor disturbances at the level of the thermoregulatory center, joints and skin, producing the major symptoms observed in our patients. However, against an endocrine theory are the facts that no endocrine abnormalities were detected in our patients; the symptoms of periodic fever, without therapy, have not changed during the lifetimes of these patients; and symptoms of periodic fever could not be reproduced when 500 cc. of whole blood obtained during a febrile episode were transfused back into the patient.

Reimann [15,16] has hypothesized that the

periodic diseases could be considered to be the extreme manifestations of some natural rhythm of life to which we are all subject.

Cortisone therapy has had a beneficial influence on the symptoms of periodic fever in all three patients personally studied. It is important to emphasize that one of the patients, Case II, since taking cortisone for ten consecutive days during the time of three consecutive attacks of fever, has obtained marked amelioration of the duration and severity of attacks for the past three years. Reimann [16-18] and Benhamou [26] have also reported beneficial effects from cortisone therapy in some of their patients. The mechanism of action of cortisone influencing the episodes of fever in this syndrome is difficult to explain, but one might speculate about a direct effect of cortisone upon the thermoregulatory center of the brain [33,34].

Periodic fever should not be considered merely a medical curiosity. A correct diagnosis is of great importance for proper medical therapy, and for satisfactory management of patients with this disease.

SUMMARY

The occurrence of periodic fever in members of five generations of the same family is described. The condition behaves as if dependent upon a dominant autosomal gene.

Cortisone therapy during the attacks of fever has been beneficial in improving the symptoms in two patients and in suppressing or markedly ameliorating the attacks in a third patient.

The importance of a correct diagnosis of periodic fever is emphasized.

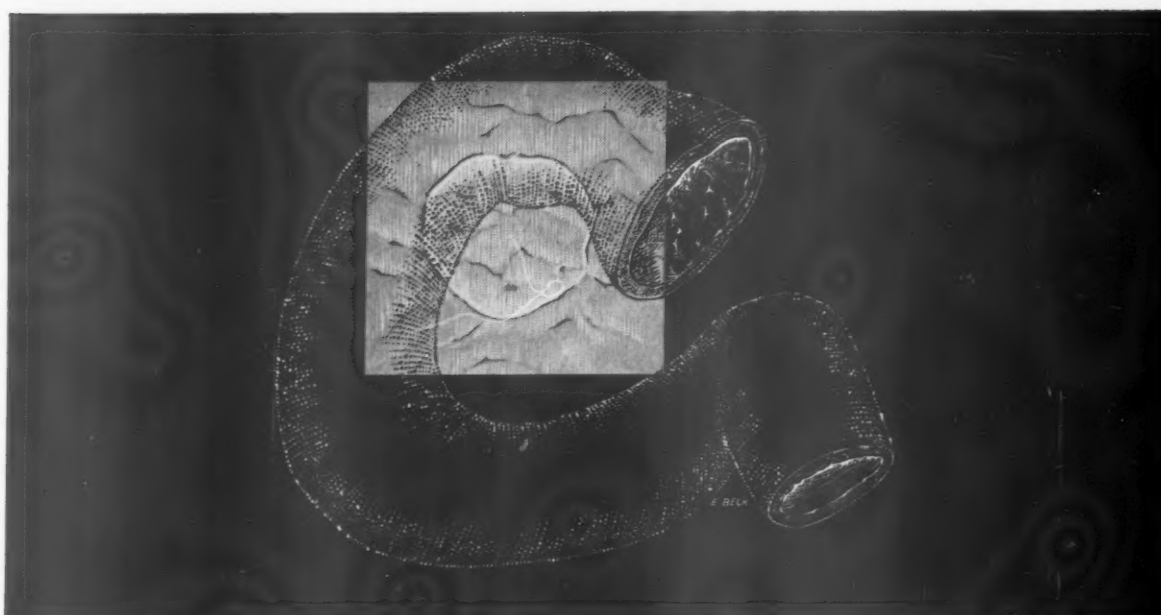
Acknowledgment: The authors express their appreciation to Dr. J. Harold Shanklin of Springfield, Ohio for referring these patients and sharing with us their medical care and to Dr. Madge T. Macklin for her suggestions.

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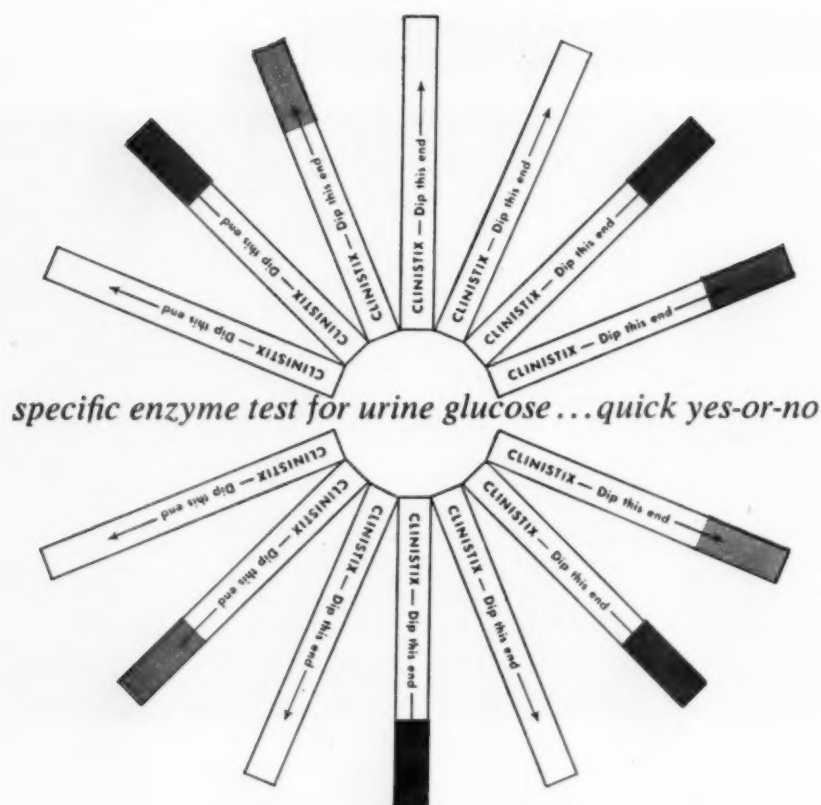
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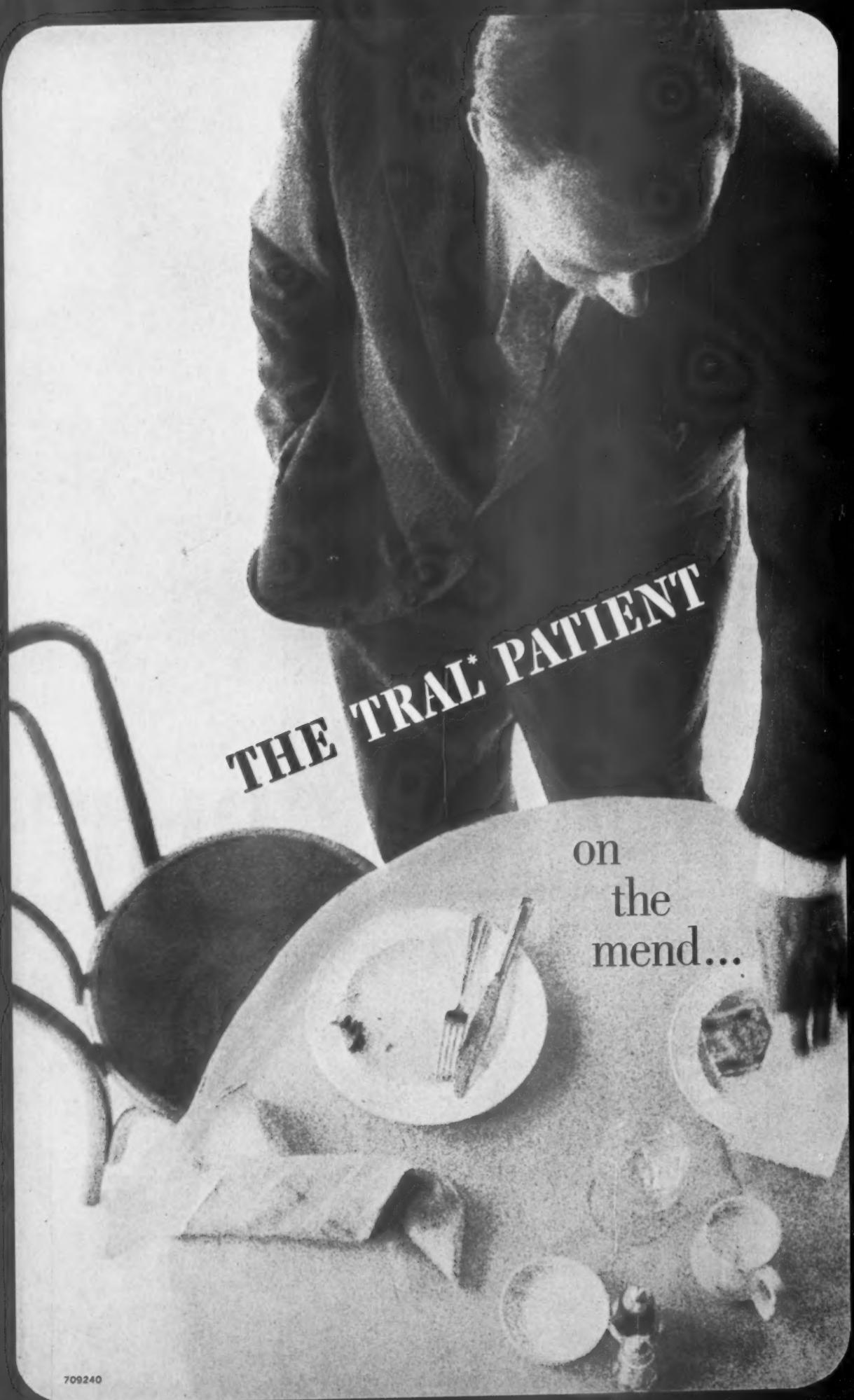
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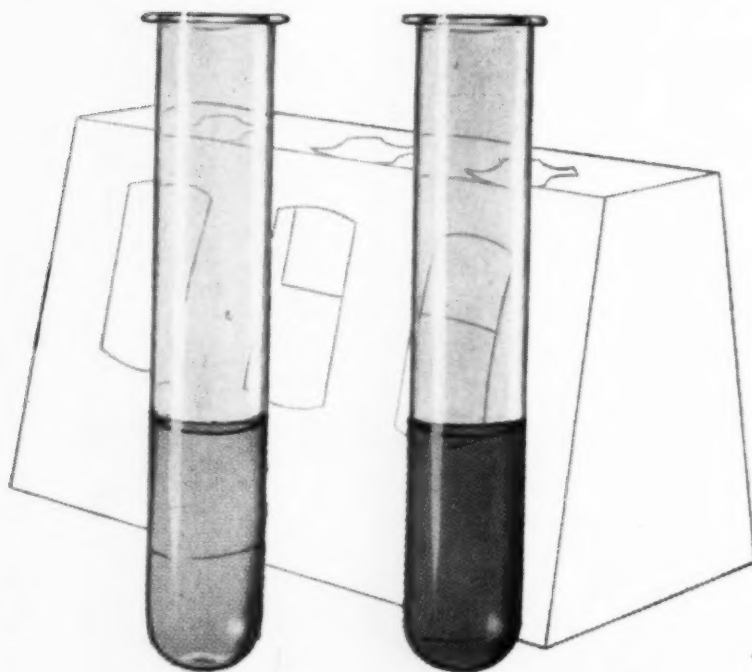


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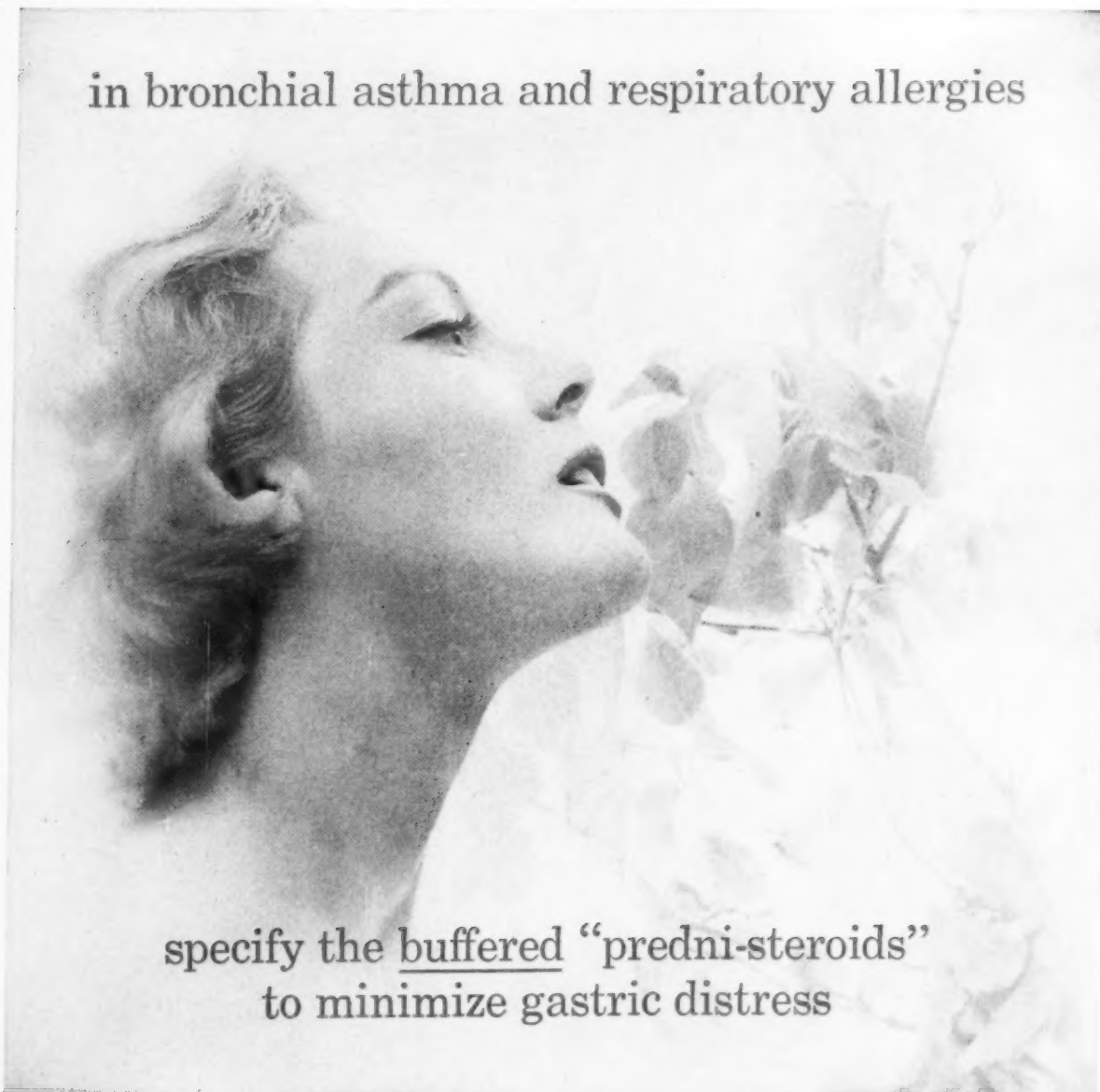
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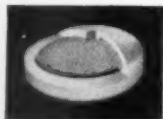
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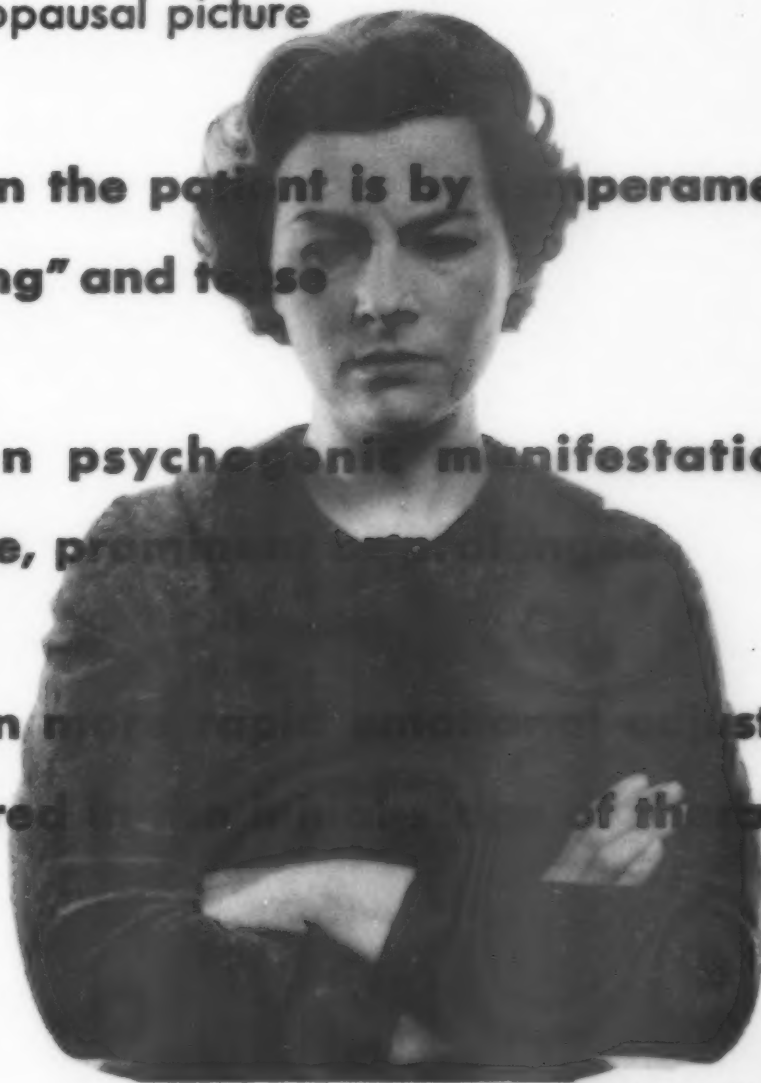
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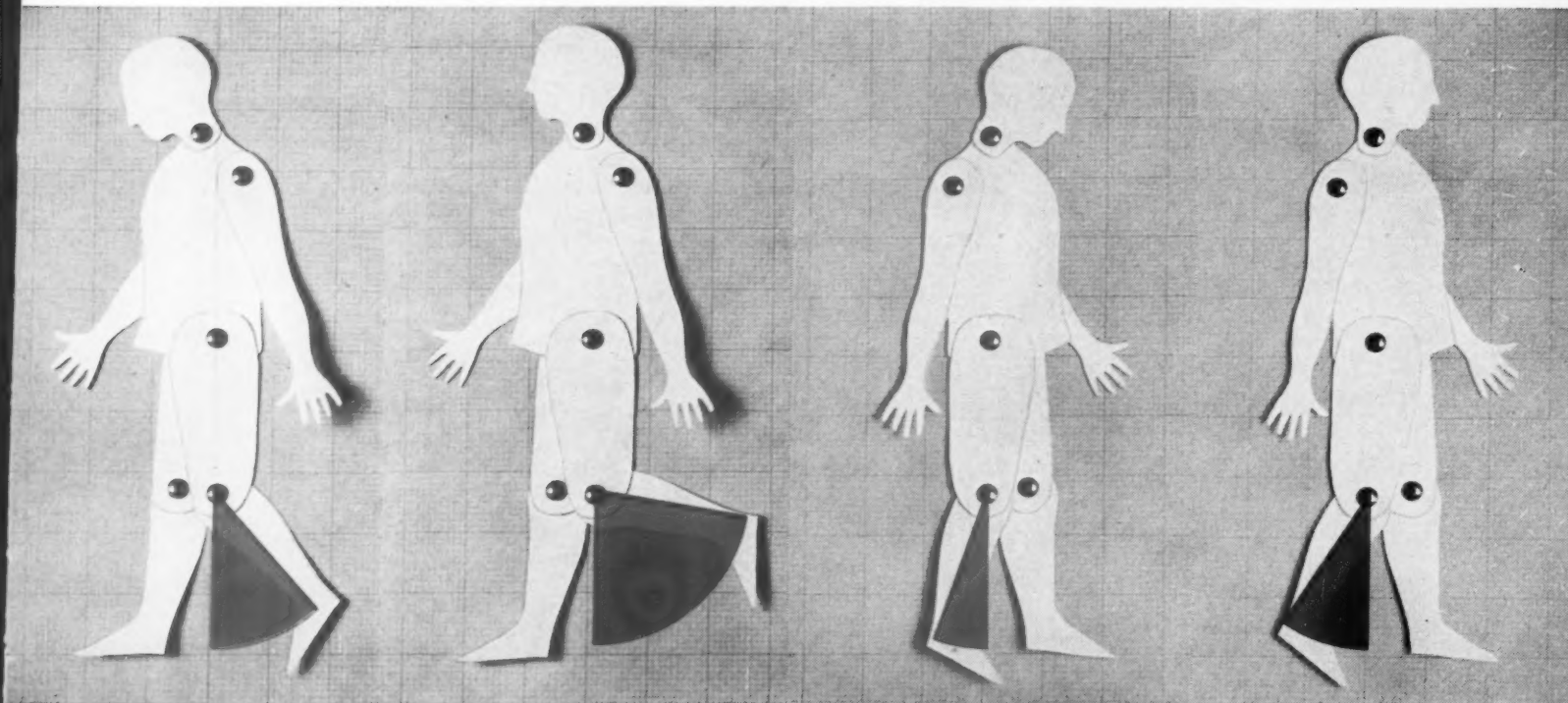
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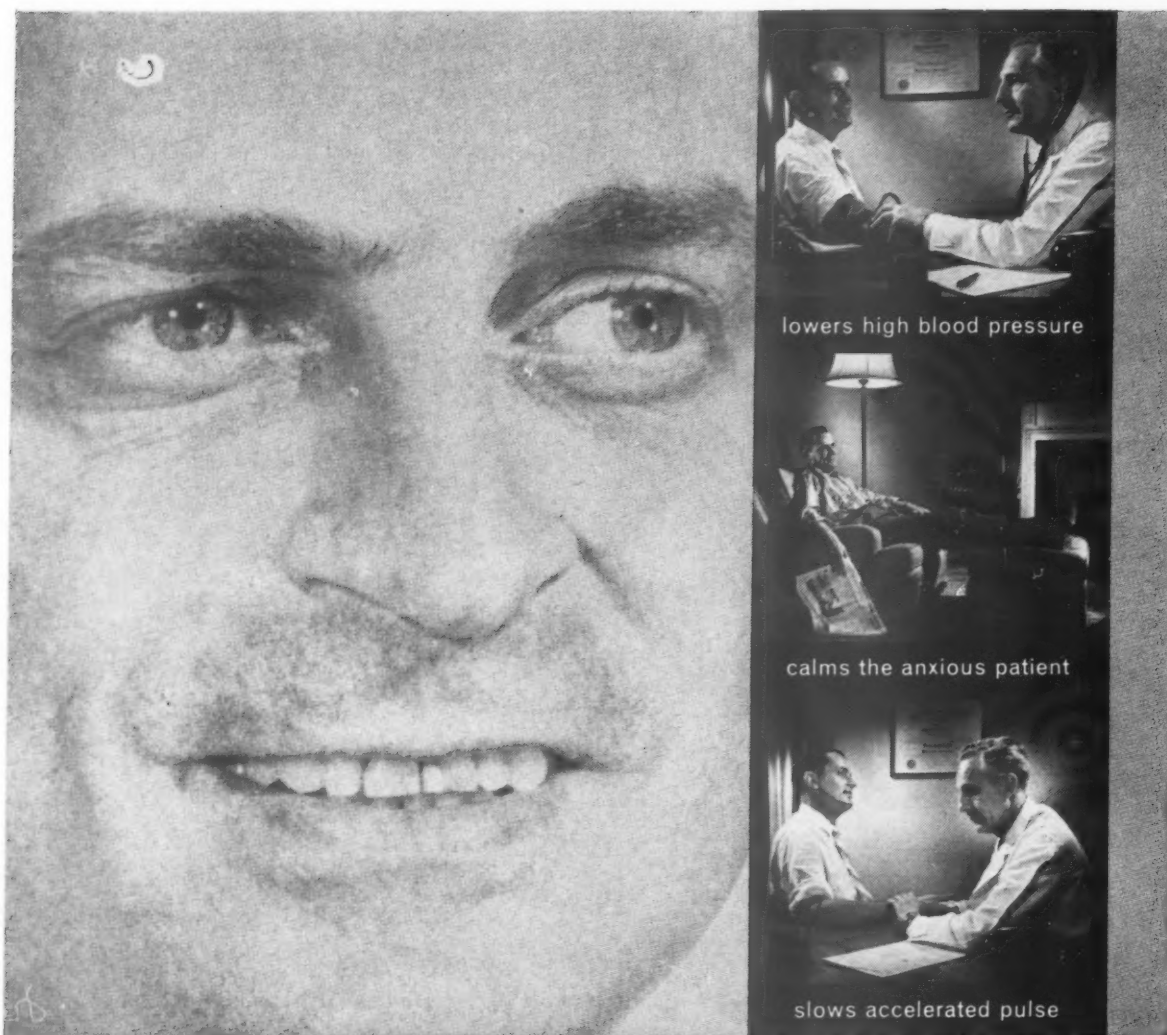


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1. Wright, W.T., Jr.; Pokorny, C., and Foster, T.L.: J. Kansas M. Soc. 57: 410 (July) 1956.

2. Moyer, J.H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. 96: 530, 1955.

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1. Cornely, D. A. and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J. A. M. A. 160:1219-1221 (April 7) 1956.

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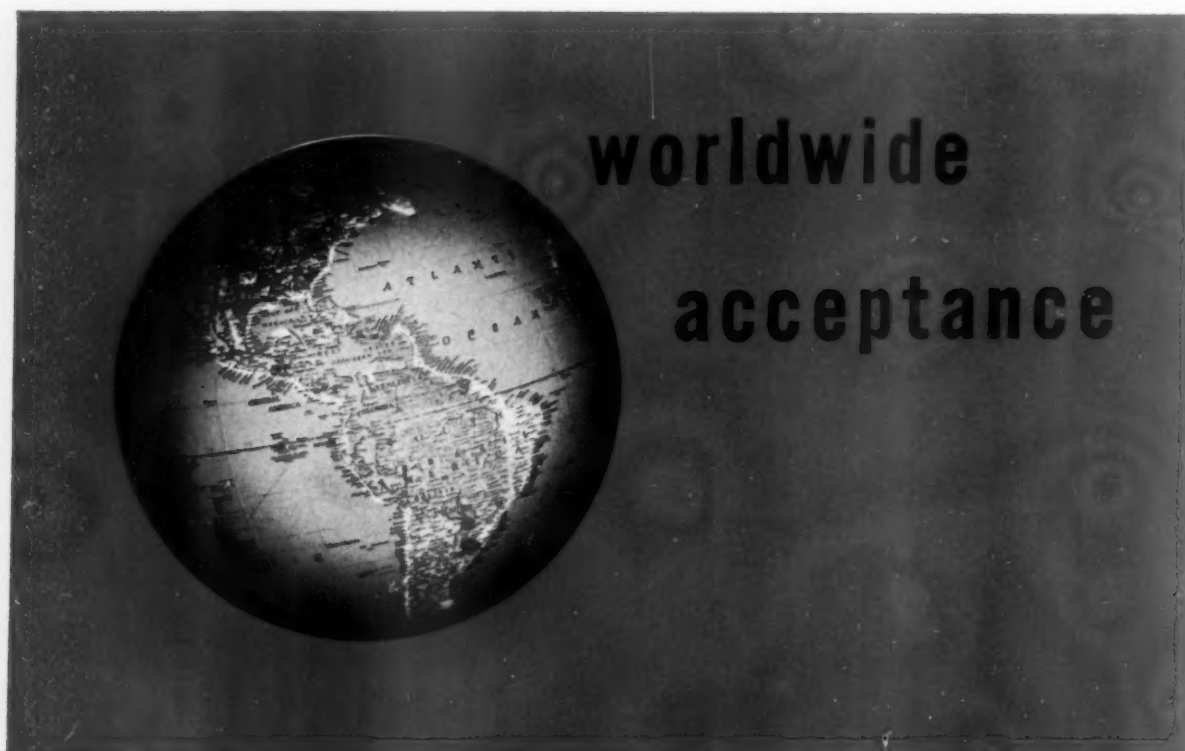
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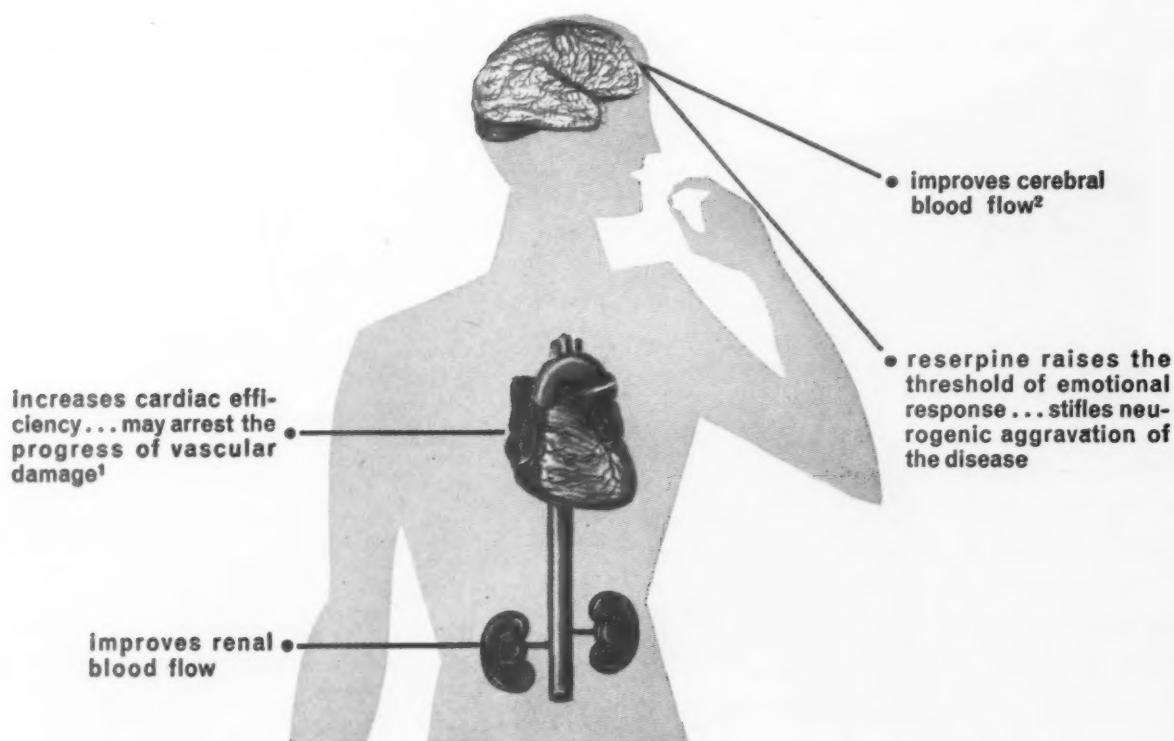
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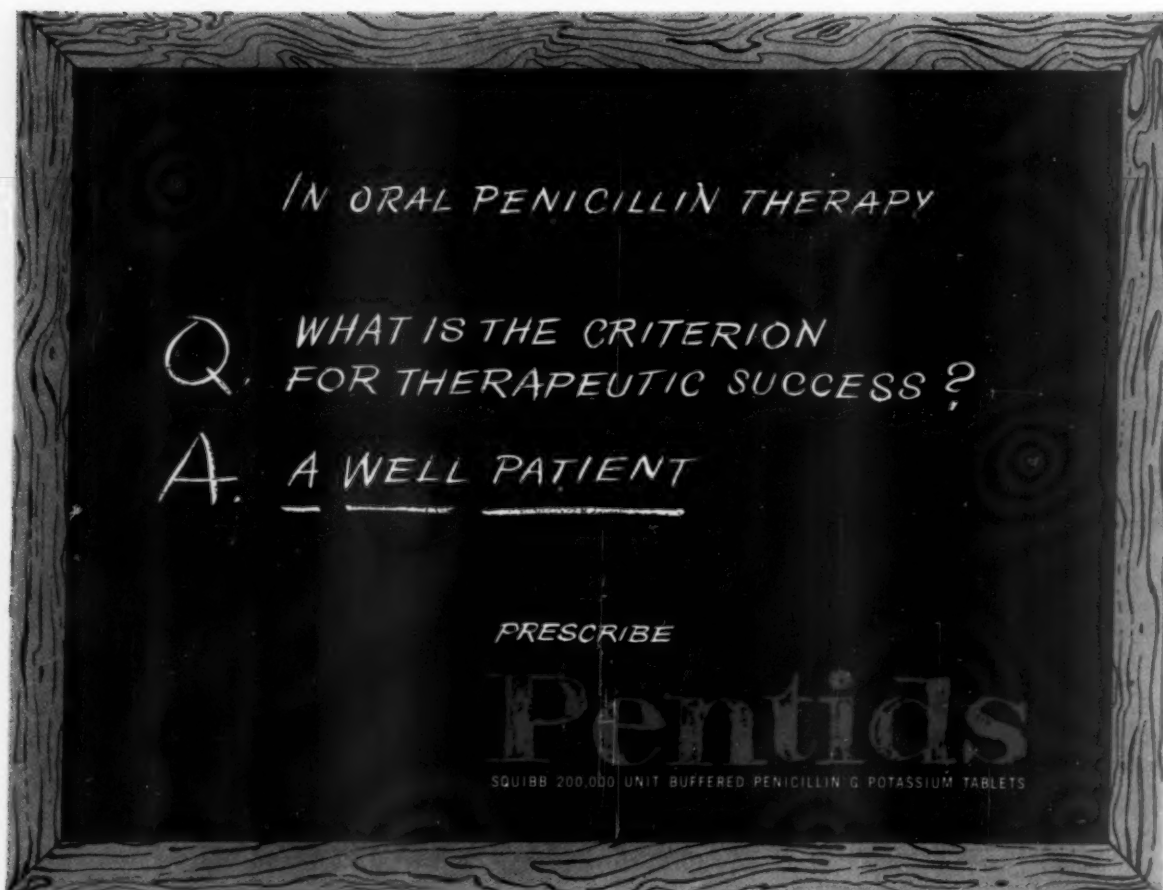
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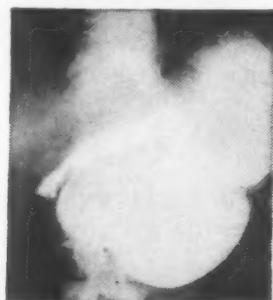
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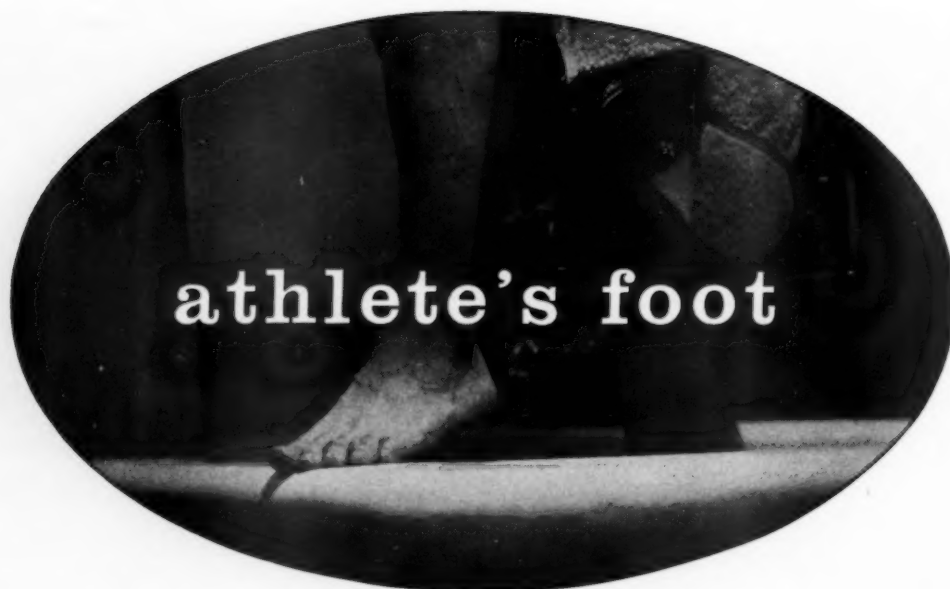
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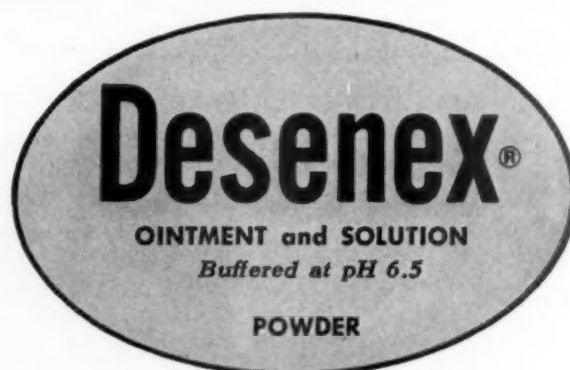
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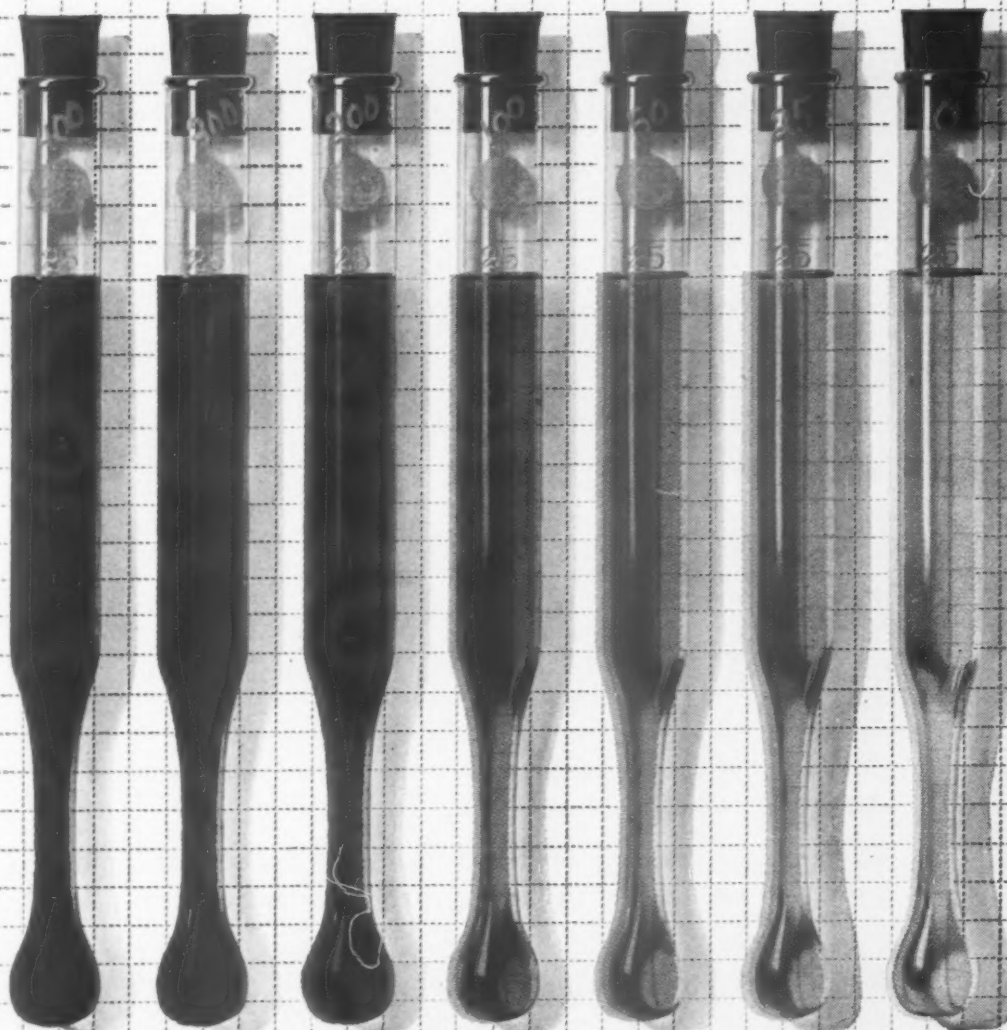
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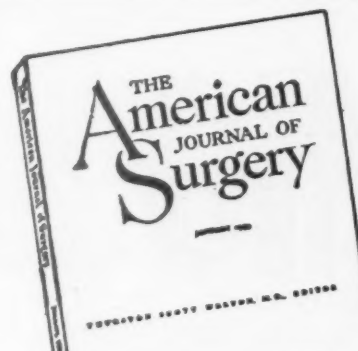
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references (1) Johnson, H. J., Jr.: To be published. (2) Settel, E.: Am. Pract. & Digest Treat. 8:443 (March) 1957. (3) New and Nonofficial Remedies, J.A.M.A. 162:205-207 (Sept. 15) 1956.

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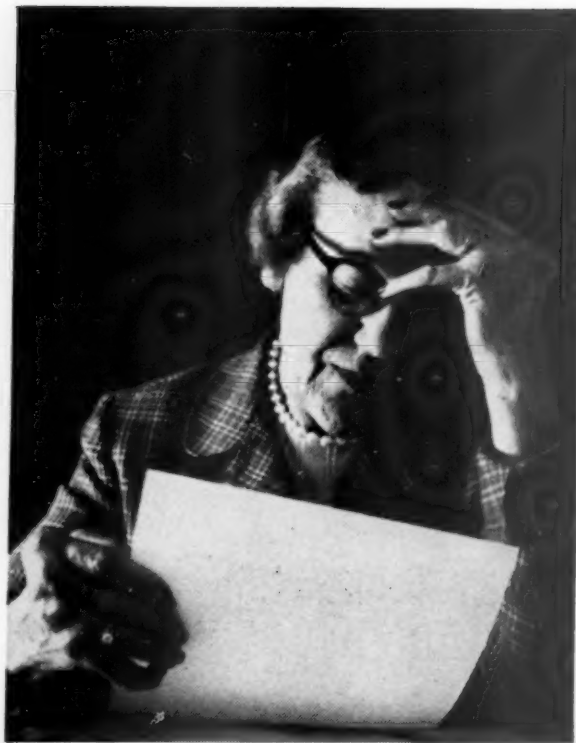
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Scherbel, A. L.: Cleveland Clinic Quarterly 24:90 (April) 1957

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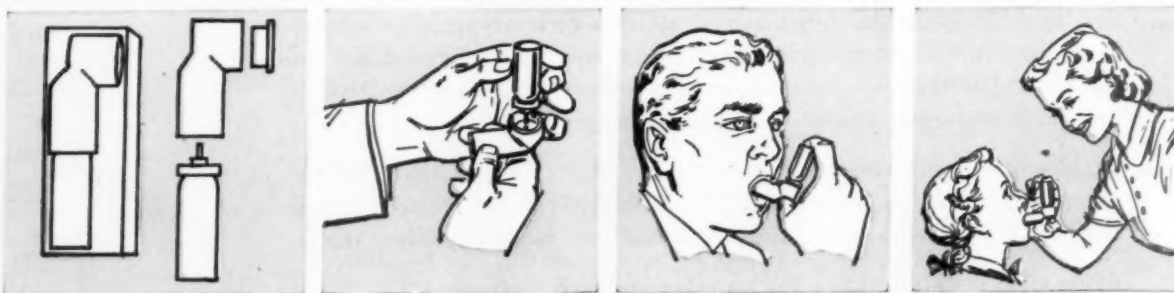
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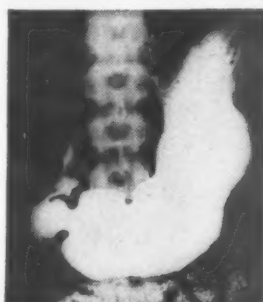
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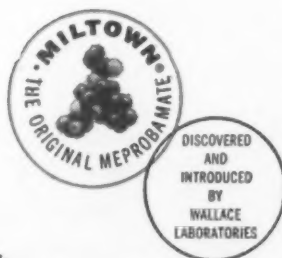
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1. Dickel, H. A., Wood, J. A. and Dixon, H. H.: Electromyographic studies on meprobamate and the working, anxious patient. *Ann. New York Acad. Sc.* **67**:780, May 9, 1957.

2. Dickel, H. A., Dixon, H. H., Wood, J. A. and Shanklin, J. G.: Electromyographic studies on patients treated with meprobamate. *West. J. Surg.* **64**:197, April 1956.



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1. Lockett, S.; Brit. M.J.
1:809 (Apr. 2) 1955.

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2. Wright, W.T., Jr., et al.; J. Kansas
M. Soc. 57:410 (July) 1956.

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